

# INTERNATIONAL STANDARDS FOR CORD BLOOD COLLECTION, BANKING, AND RELEASE FOR ADMINISTRATION ACCREDITATION MANUAL

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**Fifth Edition  
DRAFT  
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## **NOTICE**

These Standards are designed to provide minimum guidelines for Cord Blood Banks, facilities, and individuals performing cord blood donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution, or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a Cord Blood Bank, facility, or individual should implement if the standard of practice in the community or applicable law establishes additional requirements. Each Cord Blood Bank, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. The Foundation for the Accreditation of Cellular Therapy and NetCord disclaim any responsibility for setting maximum standards and expressly do not represent or warrant that compliance with these Standards is an exclusive means of complying with the standard of care in the industry or community. Further, the Foundation for Accreditation of Cellular Therapy and NetCord expressly disclaim any responsibility, liability or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to these Standards or related guidance.

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## PART A: TERMINOLOGY, ABBREVIATIONS, AND DEFINITIONS

### A1 TERMINOLOGY

For purposes of these Standards, the term *shall* means that the Standard is to be complied with at all times. The term *should* indicates an activity that is recommended or advised, but for which there may be effective alternatives. The term *may* is permissive, indicating that the practice is acceptable, but not necessarily recommended.

### A2 ABBREVIATIONS

The following abbreviations are used in these Cord Blood Standards:

<i>ABO</i>	Major human blood group including erythrocyte antigens, A, B, O
<i>C</i>	Accompany
<i>F</i>	Affix
<i>ASHI</i>	American Society for Histocompatibility and Immunogenetics
<i>T</i>	Attach
$^{\circ}\text{C}$	Degree Celsius
<i>CB</i>	Cord blood
<i>CBB</i>	Cord blood bank
<i>CBC</i>	Complete blood count (Full blood count)
<i>CB unit</i>	Cord blood unit
<i>CFU</i>	Colony forming unit
<i>DNA</i>	Deoxyribonucleic acid
<i>EFI</i>	European Federation for Immunogenetics
<i>FACT</i>	Foundation for the Accreditation of Cellular Therapy
<i>FDA</i>	United States Food and Drug Administration
<i>GVHD</i>	Graft-versus-host disease
<i>HLA</i>	Human leukocyte antigen
<i>HPC</i>	Hematopoietic progenitor cell
<i>HTA</i>	United Kingdom Human Tissue Authority
<i>IRB</i>	Institutional Review Board
<i>ISBT</i>	International Society of Blood Transfusion
$\mu\text{g}$	Microgram
<i>mL</i>	Milliliter
<i>QM</i>	Quality Management
<i>Rh</i>	Human erythrocyte antigen, Rhesus
<i>TGA</i>	Australia Therapeutic Goods Administration
<i>TNC</i>	Total nucleated cell
<i>USDA</i>	United States Department of Agriculture
<i>WMDA</i>	World Marrow Donor Association

### A3 DEFINITIONS

The definitions in this section are descriptive only. In the event of a conflict with the Standards, the Standards shall prevail.

*Accompany (C)*: To go or be together with, but not attached. Information that must accompany the cord blood unit in a sealed package may alternatively be attached or affixed.

*Adventitious agent:* Any extraneous microbiological, chemical, or radiobiological substance introduced into the cord blood unit during collection, processing, or administration.

*Adverse event:* Any unintended and unfavorable sign, symptom, abnormality, or condition temporally associated with an intervention, medical treatment, or procedure that may or may not have a causal relationship with the intervention, medical treatment, or procedure. Adverse reaction is a type of adverse event.

*Adverse reaction:* A noxious and unintended response to the collection or infusion of any cord blood unit for which there is a reasonable possibility that the cord blood unit caused the response.

*Affix (F):* To adhere in physical contact with the cord blood unit container.

*Allogeneic:* Obtained from an infant donor and intended for infusion into a genetically distinct related or unrelated recipient.

*Applicable Law:* Any local, national, or international statute, regulation, or other governmental law that is applicable to cord blood donor management including recruitment or eligibility, or to cord blood collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, or distribution that is relevant to the location or activities of the Cord Blood Bank, Cord Blood Collection Site, or Cord Blood Processing Facility.

*Aseptic technique:* Practices designed to reduce the risk of microbial contamination of products, reagents, specimens, patients, or donors.

*Associated sample:* Aliquot of biological material (e.g., blood, serum, plasma, tissue, Wharton's jelly, etc.) derived from the infant donor or maternal donor of the CB unit.

*Attach (T):* To fasten securely to the cord blood unit container by means of a tie tag or comparable alternative. Any information required to be attached to a container may alternatively be affixed.

*Audit:* Documented, systematic evaluation to determine whether approved policies, Standard Operating Procedures, or operations have been properly implemented and are being followed.

*Autologous:* Derived from and intended for the same individual.

*Available for distribution:* The time at which the cord blood unit may leave the control of the facility.

*Biohazard legend:* The universal biohazard symbol.

*Biological product deviation:* A deviation from Applicable Law, standards, or other established specifications that relate to the prevention of communicable disease transmission or cord blood unit contamination; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to cord blood unit contamination.

*Calibrate:* To set measurement equipment against a known standard.

*Calibration:* Periodic scheduled activity to check and maintain the accuracy against a known standard.

*CD34:* The 115 kD glycoprotein antigen, expressed by a small portion of cord blood cells, that is defined by a specific monoclonal antibody (anti-CD34) using the standardized cluster of differentiation (CD) terminology. Hematopoietic progenitor cells are largely contained within the CD34 cell population of cord blood units.

*Cellular therapy product:* A somatic cell-based product, including cord blood, that is procured from a donor and intended for processing and administration.

*Circular of information:* An extension of container labels that includes the use of the cord blood unit, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

*Clinical Program:* An integrated medical team that administers cord blood units.

*Colony forming unit (CFU):* A clonogenic cell able to produce hematopoietic colonies *in vitro* under specific conditions in the presence of appropriate colony stimulating factors and defined by the type of mature progeny that develop.

*Collection:* Any procedure for procuring and labeling cellular therapy products, regardless of technique or source.

*Collection kit:* Package of all materials required to collect a single CB unit. Usually intended for collection at a non-fixed CB Collection Site.

*Communicable disease:* A disease or disease agent for which there may be a risk of transmission by a cord blood unit either to a recipient or to the people who may handle or otherwise come in contact with the cord blood unit.

*Competency:* Ability to adequately perform a specific procedure or task according to directions.

*Complaint:* Any written, oral, or electronic communication about a problem associated with a distributed cord blood unit or with a service related to donor management or the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, or administration of a cord blood unit.

*Contiguous segment:* A sealed length of tubing integrally attached to the cord blood unit that contains a sample representative of the cord blood unit that may be used for testing.

*Cord blood (CB):* The infant's blood remaining in the placenta and umbilical cord after the umbilical cord has been clamped.

*Cord Blood Bank (CBB):* An integrated team under a single Cord Blood Bank Director responsible for donor management and the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of cord blood units.

*Cord blood banking (CB banking):* The processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of cord blood units intended for administration.

*Cord blood collection:* The procurement of cord blood for banking and administration before and/or after the placenta is delivered.

*Ex utero:* The collection of cord blood cells from the placental and/or umbilical cord vessels after the placenta has been delivered.

*In utero:* The collection of cord blood cells from the placental and/or umbilical cord vessels after the infant donor has been delivered and separated from the umbilical cord, but before the placenta has been delivered.

*Cord Blood Collection Site:* The location where the infant donor is delivered and the cord blood unit is collected.

*Fixed Cord Blood Collection Site:* A collection site where there is a written agreement between the collection site and the Cord Blood Bank for the collection of cord blood units over time. The agreement shall describe the interaction between the Cord Blood Collection Site and the Cord Blood Bank for all aspects of the collection process including, at a minimum, personnel training, record keeping, collection, storage, and transportation or shipping of a cord blood unit.

*Non-fixed Cord Blood Collection Site:* A collection site where there is a written agreement with a Cord Blood Bank for the collection of a single cord blood unit at the initiation of the infant donor's mother and/or family and with documentation that a health care professional has agreed to perform the collection and has training that covers each aspect of the collection process. A non-fixed Cord Blood Collection Site may collect more than one cord blood unit for the Cord Blood Bank with a written agreement for each unit.

*Cord Blood Processing Facility:* The location where cord blood processing activities are performed in support of the Cord Blood Bank. A Cord Blood Processing Facility may be part of the same institution as the Cord Blood Bank or may be part of another institution and performs these functions through contractual agreement.

*Cord blood unit (CB unit):* The nucleated cells including stem and hematopoietic progenitor cells harvested from placental and umbilical cord blood vessels from a single placenta after the umbilical cord has been clamped. HPC, Cord Blood is the proper name of a cord blood unit. Unless otherwise specified, the term cord blood unit in this document refers to any cord blood unit regardless of method of collection or intended use.

*Corrective action:* Action taken to eliminate the causes of an existing discrepancy or other undesirable situation to prevent recurrence.

*Cryopreservation:* The processing of viable cells or tissues that consists of cooling the product to a very low temperature where viability is maintained.

*Designee:* An individual with appropriate experience or expertise who is given the authority to assume a specific responsibility. The person appointing the designee retains ultimate responsibility.

*Disposition:* The current status, location, or use of a cord blood unit.

*Distribution:* Any transportation or shipment (including importation and exportation) of a cord blood unit that has been determined to meet all applicable release criteria or urgent medical need requirements.

*Donor:* A person who is the source of cells or tissue for a cellular therapy product.

*Infant donor:* The infant from whose placenta and/or umbilical cord the cord blood is obtained.

*Maternal donor:* The mother who carries the infant donor to delivery. This may be the genetic or surrogate mother.

*Unrelated donor:* The infant donor whose cord blood is collected and stored for use by a person with no known genetic relationship.

*Related donor:* The infant donor whose cord blood is collected and stored for autologous use by the donor or for allogeneic use by an individual or family that is genetically related to the donor.

*Electronic record:* Any record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer.

*Eligible:* An infant donor and/or mother who meet(s) all donor screening and testing requirements related to transmission of communicable disease as defined by Applicable Law.

*Engraftment:* The reconstitution of hematopoiesis or other cellular functions with cells from a donor.

*Errors and accidents:* Any unforeseen or unexpected deviations from Applicable Law, these Standards, or other established specifications that may affect the safety, purity, or potency of a cord blood unit.

*Establish and maintain:* A process to define, document in writing or electronically, implement, follow, review, and, as needed, revise on an ongoing basis.

*Hematopoietic progenitor cells (HPC):* Self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluri-potent progenitor cells, and committed progenitor cells, regardless of tissue source (marrow, umbilical cord blood, peripheral blood, or other tissue source).

*High resolution typing:* A high resolution typing result is defined as a set of alleles that encode the same protein sequence for the region of the HLA molecule called the antigen binding site and that excludes alleles that are not expressed as cell-surface proteins. The antigen binding site includes domain 1 and domain 2 of the class I  $\alpha$  polypeptides, and domain 1 of the class II  $\alpha$  and domain 1 of the class II  $\beta$  polypeptide chains.

*Identifier:* A numeric or alphanumeric sequence used to differentiate one item from another like item.

*Indefinitely:* A timeframe without a fixed or specified limit.

*Ineligible:* An infant donor and/or mother who does not meet all donor screening and testing requirements related to transmission of communicable disease as defined by Applicable Law.

*Institutional Review Board or Ethics Committee:* A Board or Committee established by an institution in accordance with Applicable Law to review biomedical and behavioral research involving human subjects conducted at or supported by that institution.

*ISBT 128:* The international information technology standard for transfusion medicine and transplantation. ICCBBA, Inc. ([www.iccbba.org](http://www.iccbba.org)) is the organization charged with the international maintenance of this database.

*Key personnel:* Personnel with responsibilities that significantly affect the provision, safety, and/or quality of a service or product.

*Labeling:* Steps taken to identify the original cord blood unit collection and any products or product modifications, to complete the required reviews, and to attach the appropriate labels.

*Licensed health care professional:* An individual certified by the applicable governmental agency to be competent for the duties performed.

*Linkage:* The maintenance of basic demographic information, including name, that would allow tracing of a cord blood unit to the identification of the infant donor and/or the mother.

*Listing:* The process of transferring information about a cord blood unit to be available for search.

*Low resolution typing:* A DNA-based typing result at the level of the digits comprising the first field in the DNA-based nomenclature. Examples include A\*01; A\*02. If the resolution corresponds to a serologic equivalent, this typing result should also be called low resolution.

*Manipulation:* *Ex vivo* procedure(s) that selectively removes, enriches, expands, or functionally alters hematopoietic progenitor cells.

*Materials management:* An integrated process for planning and controlling all steps in the acquisition and use of goods or supply items (materials) used for the collection or processing of cellular therapy products to determine whether these materials are of adequate quality and quantity and available when needed. The materials management system combines and integrates the material selection, vendor evaluation, purchasing, expediting, storage, distribution, and disposition of materials.

*Maternal samples:* Aliquots of cells, plasma, serum, or cellular material from the blood of the mother that can be used for testing.

*May:* Acceptable but not necessarily recommended.

*Microbial:* Related to infectious agents including bacterial and fungal organisms.

*Monitoring:* Recording quality parameters or indicators on a regular basis.

*Mother:* Any of the following:

*Birth mother:* The woman who carries the infant donor to its delivery; may be the genetic mother or a surrogate mother.

*Genetic mother:* The woman from whose egg the infant donor develops; the egg donor.

*Mother:* When used unmodified, the term mother refers to the mother who is both the genetic and birth mother.

*Surrogate mother:* The woman who carries an infant donor not genetically her own from an embryo to delivery. Under circumstances of a surrogate mother carrying the infant donor to term and the cord blood unit being collected, both the surrogate and the genetic mother shall be considered for purposes of communicable disease screening and testing; the genetic mother shall be considered for purposes of genetic information.

*Negative selection:* The manipulation of cord blood such that a specific cell population(s) is depleted.

*NetCord:* The international organization of cord blood banks that meet defined membership requirements of the International NetCord Foundation, established to promote high quality cord blood banking and clinical use of umbilical cord blood for allogeneic stem cell transplantation.

*Nonconforming cord blood unit:* Any cord blood unit that does not completely meet the requirements specified by these Standards, the Cord Blood Bank, and/or the requirements for donor eligibility as defined by Applicable Law.

*Outcome analysis:* The process by which the results of a therapeutic or technical procedure are formally assessed.

*Partial label:* The minimum essential elements that must be affixed at all times to all cord blood unit containers.



*Policy:* Document that defines the scope of an organization, explains how the goals of the organization will be achieved, and/or serves as a means by which authority can be delegated.

*Positive selection:* The manipulation of cord blood such that a specific cell population(s) is enriched.

*Potency:* The therapeutic activity of a cord blood unit as indicated by appropriate laboratory tests or adequately developed and controlled clinical data.

*Procedure:* A document that describes in detail the process or chronological steps taken to accomplish a specific task. A procedure is more specific than a policy.

*Process:* A goal-directed, interrelated series of actions, events, or steps.

*Process control:* The standardization of processes in order to produce predictable output.

*Process development:* The series of procedures performed in order to develop a final process that achieves the required results.

*Processing:* All aspects of manipulation, packaging, and labeling cord blood units, including microbial testing, preparation for storage, and removal from storage. Processing does not include collection, donor screening, donor testing, cryopreservation, storage, or distribution.

*Products:* The proper name for each class (broad descriptions of product) is as follows:\*

HPC, Cord Blood: Umbilical cord blood and/or placental blood collected as a source of hematopoietic progenitor cells.

TC, Cord Blood: Umbilical cord blood and/or placental blood collected as a source of nucleated cells. The product is intended for therapeutic use other than as HPCs.

*Proficiency test:* A test to evaluate the adequacy of testing methods and equipment and the competency of personnel performing testing.

*Protocol:* A written document describing steps of a treatment or experimental procedure in sufficient detail such that the treatment or procedure can be reproduced repeatedly without variation.

*Purity:* Relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.

*Qualification:* The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.

*Quality:* Conformance of a product or process to pre-established specifications or standards.

*Quality assessment:* The actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

*Quality assurance:* The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected individually and collectively.

*Quality audit:* A documented, independent inspection and review of a facility's activities. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

*Quality control:* A component of a quality program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of cord blood units, including testing and product release.

*Quality improvement:* The actions, planned and performed, to develop a system to review and improve the quality of a product or process.

*Quality Management (QM):* An integrated program of quality assessment, assurance, control, and improvement.

*Quality Management Plan:* A written document that describes the systems in place to implement the Quality Management Program.

*Quality Management Program:* An organization's comprehensive system of quality assessment, assurance, control, and improvement. A Quality Management Program is designed to prevent, detect, and correct deficiencies that may adversely affect the quality of the cord blood unit or increase the risk of communicable disease introduction or transmission.

*Quality Management Supervisor:* A qualified individual approved by the Cord Blood Bank Director to establish methods to review, modify, approve, and implement all Standard Operating Procedures related to Quality Management and to monitor compliance with these Standards.

*Quarantine:* The segregation of a cord blood unit to prevent cross-contamination or improper release. Quarantine can be temporal, physical, or a designation within the cord blood unit record.

*Recipient:* The individual into whom the cord blood unit was transplanted.

*Reference samples:* Aliquots of cells, plasma, serum, or cellular material from the cord blood unit, the umbilical cord, or the placenta that can be used to confirm the identity, HLA typing, or genetic or communicable disease information associated with a single cord blood unit. Such samples may or may not be contiguous segments.

*Registry:* An organization that publishes or makes available the description of cord blood units available for administration and may conduct searches of the available cord blood units, either exclusively or in conjunction with the Cord Blood Bank as defined in their agreement.

*Release:* The removal of a cord blood unit from quarantine or in-process status when it meets specified criteria.

*Reservation:* A temporary allocation of a cord blood unit to a specific recipient to prevent consideration of that cord blood unit for another recipient.

*Retention sample:* An aliquot replicate of the final cord blood unit.

*Rh:* The abbreviation for the Rhesus system of human red cell antigens; is used in this document to refer to the Rh (D) antigen only unless otherwise specified.

*Safety:* Relative freedom from harmful effects to persons or products.

*Search:* The process used to produce a report of cord blood units that are potential matches for a recipient.

*Selection:* The process of identification of a donor or cord blood unit according to defined criteria.

*Shall:* To be complied with at all times.

*Shipping:* The physical act of transferring a cord blood unit within or between facilities during which the unit leaves the control of trained personnel at the distributing or receiving facility.

*Should:* Recommended or advised, but effective alternatives may exist.

*Significant warming event:* Any event when a cryopreserved cord blood unit reaches  $-120^{\circ}\text{C}$  or warmer during the life of the cryopreserved cord blood unit.

*Standard Operating Procedure:* Written detailed instructions required to perform a procedure.

*Standard Operating Procedures Manual:* A compilation of the current Standard Operating Procedures.

*Standards:* The current edition of the *International Standards for Cord Blood Collection, Banking, and Release for Administration* published by NetCord and FACT.

*Sterility testing:* The processes used to screen for the presence of microbial agents.

*Storage:* Holding cord blood units for future processing and/or distribution.

*Suitability:* The maternal and infant donor's medical fitness to undergo the cord blood collection procedure.

*Time of collection:* The time of day that the cord blood collection is completed.

*Total nucleated cell (TNC) count:* The number of cells with a nucleus or nuclei in a cord blood unit.

*Trace:* To follow the history of a process, product, or service by review of documents.

*Track:* To follow a process or product from beginning to end.

*Transplantation:* The infusion of allogeneic or autologous cord blood cells with the intent of providing transient or permanent engraftment in support of therapy for disease.

*Transport:* The physical act of transferring a cord blood unit within or between facilities. During transportation the product does not leave the control of trained personnel at the transporting or receiving facility.

*Unique:* Being the only one of its kind or having only one use or purpose.

*Unique Identifier:* A numeric or alphanumeric sequence used to designate a specific cord blood unit with reasonable confidence that the identifier will not be used for another purpose, including for another cord blood unit.

*Urgent medical need:* A situation in which no comparable cord blood unit is available and the recipient is likely to suffer death or serious morbidity without the cord blood unit.

*Validation:* Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process is validated by establishing, by objective evidence, that the process consistently produces a cord blood unit meeting its predetermined specifications.

*Variance:* A deviation from recommended practice or Standard Operating Procedure.

*Verification:* The confirmation of the accuracy of something or that specified characteristics have been fulfilled.

*Verification typing:* HLA typing performed on an independent sample (or, for a cord blood unit, from an attached segment or from the unit itself) with the purpose of verifying concordance of that typing assignment with the initial HLA typing assignment. Concordance does not require identical levels of resolution for the two sets of typing but requires the two assignments to be consistent with one another.

*Viability:* Living cells as defined by dye exclusion, flow cytometry, or progenitor cell culture.

*Written:* Documentation in human readable form.

*\*These definitions are as of publication. The current terminology in Chapter Three of the ICCBBA document, "ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions," is required. This document can be found at <http://www.iccbba.org> > Subject Area > Cellular Therapy > Standard Terminology.*

**PART B: CORD BLOOD BANK OPERATIONAL STANDARDS**

**STANDARD:**

**B1 GENERAL REQUIREMENTS**

*B1.1 The Cord Blood Bank (CBB) shall consist of an integrated team, under a single CBB Director, responsible for donor management; collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of cord blood (CB) units; and recipient follow-up.*

**Explanation:**

The Cord Blood Bank (CBB) is an inclusive program that is responsible for the entire process from donor recruitment to cord blood (CB) unit distribution, with outcome analysis. If there are shared responsibilities among multiple organizations, it is the responsibility of the CBB to require all parties involved to be in compliance with these Standards as they pertain to the shared responsibilities.

If a standard does not specify the type of donation, it applies to both unrelated and related CB units. **Figure 1: Specified Requirements for Unrelated and Related Cord Blood Units** outlines standards that are specifically for unrelated or related CB units to assist CBBs with understanding when a standard may or may not apply depending on their business models. Standards that apply to both unrelated and related CB units are not included in this table, nor are the differences in the requirements included in the appendices.

**Figure 1: Specified Requirements for Unrelated and Related Cord Blood Units**

<b>Subject</b>	<b>Unrelated CB Units</b>	<b>Related CB Units</b>
Return of CB Units to Inventory	B9.5.1, E5.5	B9.5.2
Informed Consent	C4.6.6.1	C4.6.6.2
History of Genetic or Malignant Disease	C5.3.1.6	
Ineligible CB Units	C5.3.5	
<i>In utero</i> Collection	C6.2.3	C6.2.4
CB Acceptance Criteria	D4.1.2	D4.1.3
Cryopreservation	D4.2.6	D4.2.7
Warming Events	D7.5.2.2	
CB Unit Disposal		D9.3.3, D9.3.3.1, D9.3.3.2
Microbial Cultures	D10.3.2.1	D10.3.2.2
CB Unit Listing	E2.2	E1.2
Data for Clinical Program		E3.4.1.1, E3.4.3.1

**STANDARD:**

*B1.2 The CBB, each CB Collection Site, and each CB Processing Facility shall operate in compliance with Applicable Law and these Standards.*

- B1.2.1 The CBB shall be licensed, registered, and/or accredited as required by the appropriate governmental authorities for the activities performed.*
- B1.3 The CBB shall have a mechanism to list and distribute CB units for clinical use.*
- B1.3.1 If the CBB utilizes a registry to deliver services related to the listing, search, selection, reservation, release, and/or distribution of a CB unit:*
- B1.3.1.1 The responsibilities of the registry shall be clearly documented.*
- B1.3.1.2 The registry shall comply with these Standards as applicable to its responsibilities.*
- B1.3.1.3 The registry should be accredited by the WMDA.*
- B1.4 If the CBB contracts with any other entity for services related to CB unit donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, and/or any other aspect of banking, the responsibility of each entity shall be clearly documented.*
- B1.4.1 Each participating entity shall meet these Standards with respect to its interactions with the CBB.*

**Explanation:**

The Standards are not intended to dictate specific CBB structures or business practices. Processing and/or collection services may be contracted with other services as desired as long as the responsibilities of each service are well documented. Accreditation by FACT-NetCord, however, does require that any CBB must use collection, banking, and release for administration services that meet the Standards. There is no partial accreditation for these services individually; each entity performing all or part of these services must be inspected in relation to their activities with the CBB.

The Standards apply to CB units collected for related use (autologous and/or related allogeneic), and unrelated allogeneic use unless specifically stated otherwise. Related use includes those units for which there is a known intended recipient or family. Unrelated use is a donation to a bank from which transplant physicians can select a unit based upon its suitability for a patient unrelated to the donor.

Section B of these Standards pertains to the entire CBB and each of its CB Collection Sites and CB Processing Facilities.

**Evidence:**

If a CBB works with a registry or external facility that performs specified functions, the responsibilities of each must be clearly outlined in a written agreement.

Documentation that entities performing contracted services in donor management, collection, processing, cryopreservation, and storage meet the Standards requires successful completion of an on-site inspection. Registries used by the CBB should be accredited by the WMDA; if not, the CBB must provide evidence that the registry complies with the Standards as applicable to its responsibilities and an explanation for why it chooses to utilize a registry that is not accredited by the WMDA.

**STANDARD:**

*B1.5 There shall be a CBB Director, a CBB Medical Director, a CB Collection Site Director, a CB Processing Facility Director, and a Quality Management (QM) Supervisor.*

*B1.5.1 The CBB Director shall have an earned doctoral degree in medicine or in a related scientific field, with training and a minimum of two (2) years of experience in immunogenetics of transplantation, basic or clinical immunology, immunohematology, basic or clinical hematology, transfusion medicine, blood or tissue banking, or cryobiology. The CBB Director has final responsibility for the CBB operations and its overall compliance with these Standards, including all components of the CBB's policies and Standard Operating Procedures. The CBB Director shall participate regularly in educational activities related to the field of CB banking and/or cellular therapy product collection, processing, and transplantation.*

*B1.5.1.1 If the CBB Director does not have specific training and expertise in HLA, the CBB shall confirm HLA expertise is available and utilized by the CBB.*

**Explanation:**

The CBB Director's expertise must extend to the use of CB units for clinical transplantation and/or regenerative medicine. The Director must have training and a minimum of two years of experience in the fields listed in this standard.

Furthermore, the CBB Director has final responsibility for the HLA typing, listing, search, selection, reservation, release, and distribution of the CB units and must have HLA typing expertise or confirm that such expertise is available to the CBB.

The CBB Director is responsible for the entire process of cord blood collection, banking, and release for administration and has a hierarchical lead over the CB Collection Site Director and CB Processing Facility Director for all activities related to cord blood donor management and collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, and distribution of CB units.

If the CBB has an IRB, the CBB Director is responsible for it as part of his/her responsibility for compliance with Applicable Law and clinical performance.

**Evidence:**

The CBB will be asked to submit documentation of the CBB Director's degree, evidence of training, years of experience, and publications. Given the growing uses of CB units, CBB

Directors may come from a wide range of professional and/or medical backgrounds. If the qualifications of a CBB Director are unclear, the Accreditation Committee will review the documentation and make a recommendation to the FACT and NetCord Boards of Directors.

**Example(s):**

Typically, the HLA typing responsibilities are delegated to the HLA testing laboratory and the CBB Director is responsible for ensuring that the typing is done correctly, the results match the original typing results (for verification typing), and that the results meet release criteria. The CBB may also delegate the HLA typing responsibilities to experts from a national registry. Many different arrangements may satisfy this requirement as long as there is an individual with the appropriate training and expertise responsible for this aspect of CB banking.

**STANDARD:**

*B1.5.2 The CBB Medical Director shall be a licensed physician with training in hematopoietic cell transplantation or blood or tissue banking. This individual is responsible for donor recruitment; donor eligibility; medical aspects of CB collection procedures, CB processing procedures, and review of the release and administration of the CB unit; and compliance of the CB Collection Sites and CB Processing Facilities with these Standards. The CBB Medical Director shall participate regularly in educational activities related to the field of donor safety, CB banking, and/or cellular therapy product collection, processing, and transplantation.*

*B1.5.2.1 The CBB Medical Director may also serve as the CBB Director, CB Collection Site Director, and/or CB Processing Facility Director if appropriately credentialed.*

**Explanation:**

The CBB Medical Director is responsible for medical aspects of cord blood collection, banking, and release. Part of this responsibility is to review information from Clinical Programs regarding the medical aspects of the administration of the CB unit. As a physician, the CBB Medical Director has the expertise to review the data and determine if a unit is potentially responsible for any adverse events.

**Evidence:**

Documentation that would provide evidence of a CBB Medical Director's responsibilities includes a job description, attendance at meetings, signatures on forms and reports, etc.

**STANDARD:**

*B1.5.3 The CB Collection Site Director shall be a health care professional who is responsible for communicating with the CBB Medical Director regarding operations at an individual CB Collection Site. The CB Collection Site Director shall participate regularly in educational activities related to the field of donor safety, CB banking, and/or cellular therapy product collection, processing, and transplantation.*



*B1.5.3.1 The CBB Medical Director may serve the function of the CB Collection Site Director and need not be licensed in the jurisdiction of the CB collection or be on the staff of the CB Collection Site.*

**Explanation:**

The CB Collection Site Director must maintain communication between the CBB and each CB Collection Site he/she is responsible for. A different CB Collection Site Director for each site is not required; one person can direct multiple sites.

**Example(s):**

A CB Collection Site Director may be a licensed health care professional or a health care administrator.

**STANDARD:**

*B1.5.4 The CB Processing Facility Director shall be an individual with a relevant doctoral degree, qualified by training or experience for the scope of activities carried out in the CB Processing Facility. The CB Processing Facility Director is responsible for all operational aspects of all procedures related to receipt, testing, processing, cryopreservation, storage, release, and distribution of CB units and administrative operations of the CB Processing Facility, including compliance with these Standards. The CB Processing Facility Director shall participate regularly in educational activities related to the field of CB banking and/or cellular therapy product collection, processing, and transplantation.*

*B1.5.4.1 The CB Processing Facility Director may also serve as the CBB Director and/or CBB Medical Director if appropriately credentialed.*

**Explanation:**

The CB Processing Facility Director should be experienced in blood, progenitor cell, or tissue processing for clinical use and needs to be qualified in aspects such as traceability, volume reduction, cellular qualification, virology testing, cryobiology, long-term storage facilities, and distribution for human administration.

**STANDARD:**

*B1.5.5 The QM Supervisor shall be an individual with relevant training in quality management and approved by the CBB Director to establish and maintain systems to review, modify as necessary, approve, and implement all policies and Standard Operating Procedures intended to monitor performance of the CBB, the quality of the CB units, and compliance with these Standards.*

**Explanation:**

The QM Supervisor must have training relevant to establishing and maintaining QM activities. The QM Supervisor is responsible for establishing and maintaining policies and procedures that are used to monitor the CBB's processes in relation to the quality of the CB units and compliance with these Standards.

An appropriately developed QM Program will allow a QM Supervisor with sufficient training in the process to collect, review, and summarize the results of the QM activities. This individual should oversee the QM activities to verify they are performed properly and the data collected are used to improve processes.

**Example(s):**

In the U.S., the FDA guidance, "Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications," states that the department (referred to by the FDA as the "Quality Control Unit") has the responsibility and authority to approve/reject all components, drug product containers and closures, in-process materials, packaging, labeling, and CB units (21 CFR 211.22(a)). This guidance is available at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf>.

**STANDARD:**

*B1.5.5.1 The QM Supervisor shall be a different individual from the CBB Director, CBB Medical Director, CB Collection Site Director, and the CB Processing Facility Director.*

**Explanation:**

CBBs must minimize conflicts of interest of the QM Supervisor as required by Applicable Law.

**Example(s):**

QM Supervisors typically come from a variety of backgrounds and are not required to have QM training within a specific field. On-site QM training is also acceptable.

**STANDARD:**

*B1.5.5.2 The QM Supervisor shall not have oversight of his/her own work if this person also performs other tasks in the CBB.*

*B1.5.5.3 The QM Supervisor shall participate regularly in educational activities related to the field of quality management, CB banking, and/or cellular therapy product collection, processing, and transplantation.*

*B1.5.6 The CBB shall have an adequate number of qualified staff for its operations.*

**B2 QUALITY MANAGEMENT**

*B2.1 The CBB shall establish and maintain a QM Program that includes all key CBB functions including donor management, collection, processing, testing,*

*cryopreservation, storage, listing, search, selection, reservation, release, distribution, and outcome analysis.*

*B2.1.1 The CBB shall establish and maintain a written QM Plan that describes the QM Program.*

**Example(s):**

QM Plans can be approached and formatted in a number of ways. For instance, a CBB may outline its plan according to the FDA's GTPs or GMPs, an ISO system format, or according to these Standards. Regardless of the format selected, the CBB needs to demonstrate that all key areas of QM are addressed. If any components of the CBB's plan are part of a larger entity's program, e.g., occupational health and safety training, the CBB must demonstrate that the records of training and results of evaluations are referred back to the CBB.

**STANDARD:**

*B2.1.2 The CBB Director and the QM Supervisor shall participate in the establishment and maintenance of the QM Plan.*

*B2.1.2.1 The QM Supervisor shall have authority over and responsibility for ensuring the QM Program is effectively established and maintained.*

*B2.1.3 The QM Supervisor shall report on quality management activities, at a minimum, quarterly.*

*B2.1.4 The QM Supervisor shall report on the performance of the QM Program on an annual basis, at a minimum.*

**Explanation:**

There must be a designated person to oversee the QM Program. The ultimate responsibility for performance of the QM Plan and monitoring of all QM Program elements, internal or contracted, is that of the CBB Director. This includes reviewing key performance data across collection, processing, release for administration, and clinical outcomes.

The day-to-day tasks of the QM Program, however, may be delegated to an individual within the CBB with sufficient expertise, such as the QM Supervisor. The designated person must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each occurrence while others may be prospectively analyzed and reported at defined intervals. The data should be analyzed and assessed for improvement opportunities on a regular basis, such as at each QM meeting. Strategies to effect improvement should be identified and implemented. The results of the implemented strategies should be measured and the improvement strategies either continued or new alternatives developed depending on the results.

In addition, an annual review and report on the overall performance of the QM Plan must be performed by the CBB Director. The annual report must provide a year-long view of the overall

function of the QM Plan, its effect on and interactions with the CB Collection Sites and CB Processing Facilities, and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

**Evidence:**

QM Program meeting records should provide evidence of the CBB Director's involvement.

**Example(s):**

A designee for QM activities can be a member of another department, such as an institutional Quality Assessment and Improvement Department, who devotes some time to the QM activities of the CBB, or he/she could be a member of CBB personnel. The staff conducting the quality assessment audits may be the designated supervisor or another staff member, but it must not be the staff member who performed the work under review, unless performed in a retrospective fashion with enough delay between the time the work was performed and the time it is audited to mitigate bias. The same person may be responsible for QM of all components of the CBB or each component may have a distinct individual responsible for QM, as long as there is a mechanism for disbursement of information to all participating entities.

Quarterly reports can be based around minutes from the regular quality management meetings (if the frequency of the meetings is sufficient) and should summarize activities such as training performed, documents reviewed, audits performed, and procedures introduced or amended.

CBB Directors may wish to report on the performance of the QM Plan more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Plan is functioning over time.

**STANDARD:**

*B2.2 The QM Plan shall include, or summarize and reference, documentation of the relationship and interaction among all participating facilities and services, including, at a minimum, CB Collection Sites, CB Processing Facilities, IT services, testing laboratories, storage facilities, registries, and outcomes databases.*

**Example(s):**

This documentation may be in an organizational chart or other method that clearly illustrates the relationship and interaction among all participating facilities and services.

**STANDARD:**

*B2.2.1 The QM Plan shall include, or summarize and reference, an organizational chart of key positions, functions, and interactions within the CBB, the CB Collection Sites, and the CB Processing Facility.*

**Explanation:**

In a CBB with unrelated CB units, where collection is routine, oversight responsibility should be coordinated by a particular individual at the CBB or at the CB Collection Site, who reports to the CBB Medical Director.

A description of how key personnel interact to implement QM activities is particularly important in non-fixed CB Collection Sites, or those sites not staffed by CBB personnel, where the lines of communication may not be as clear as in CBBs who staff their own CB Collection Sites.

**Evidence:**

There shall be a clear mechanism whereby health care professionals at non-fixed CB Collection Sites communicate with the CBB Medical Director.

**STANDARD:**

*B2.3 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for establishment and maintenance of written agreements with external parties whose services impact the CB unit.*

*B2.3.1 Agreements shall include the responsibility of the external party performing any relevant aspect of CB collection, testing banking, or distribution for administration to comply with Applicable Law, these Standards, and the requirements of other applicable accrediting agencies.*

*B2.3.2 Agreements shall be dated and reviewed on a regular basis.*

**Explanation:**

Written agreements are required for individuals and/or organizations that are external to the CBB but perform services that impact CB units. This is different from designees, who are typically personnel within the CBB who have been delegated responsibilities for which they have the appropriate training and expertise.

**Example(s):**

For example, if the HLA typing review is the responsibility of a registry, the CBB must outline this in a written agreement; if the HLA typing is delegated to the CB Processing Facility Director because he/she has the necessary training and expertise, a written agreement is not required.

**STANDARD:**

*B2.4 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for personnel education, experience, and training requirements for each key position in the CBB. Personnel requirements shall include at a minimum:*

**Explanation:**

These personnel requirements are intended for key personnel who perform tasks related to the actual CB units. Clerical staff is not required to meet these requirements.

**STANDARD:**

*B2.4.1 Current position description for each staff member.*

*B2.4.2 A system to document for each staff member:*

- B2.4.2.1 Initial qualifications.*
- B2.4.2.2 Orientation.*
- B2.4.2.3 Initial training, training on each procedure performed, and retraining as necessary.*
- B2.4.2.4 Competency for each function performed.*
- B2.4.2.5 Continued competency at least annually.*
- B2.4.2.6 Annual performance review.*
- B2.4.2.7 Continued education.*

**Explanation:**

Continued training and retraining includes instances where a new or revised SOP is implemented. Personnel must be trained on those changes prior to actually performing the new or revised procedure. This does not mean that the SOP cannot be implemented until all personnel have been trained, but that an individual personnel member cannot perform the procedure until he/she actually has been trained.

**Evidence:**

The CBB must show the inspector the process for documenting annual performance reviews; however, inspectors do not need to review actual performance issues beyond competency.

**Example(s):**

For example, a new or revised SOP can be implemented while a member of the staff is on maternity leave, but that member must be trained upon her return before performing the procedure.

Training for laboratory technicians may include participation in proficiency testing in key areas.

**STANDARD:**

- B2.4.3 Trainer and training requirements for each position in the CBB, including at a minimum:*
  - B2.4.3.1 A policy and/or Standard Operating Procedure for personnel training and competency assessment.*
  - B2.4.3.2 A system that provides consistent training programs.*
  - B2.4.3.3 A description of minimal trainer qualifications.*

**Explanation:**

CB banking is a specialized field and there will not often be relevant “train-the-trainer” courses available to allow personnel to become qualified as trainers of new staff members. The QM Plan should describe how CBB personnel become qualified to act as trainers.

**Evidence:**

The criteria for selection and training of trainers/assessors should be clearly defined.

**Example(s):**

Trainer requirements may be based on experience and continued demonstrated competency and may include formal training using external courses.

**STANDARD:**

*B2.4.4 Records of identification codes of personnel including methods to link the name and/or signature to the initials or other codes used to identify the responsible staff member. These records shall include dates of employment.*

**Explanation:**

This standard is relevant to all staff members who are responsible for signing documents related to the CB unit at any stage, including, but not limited to, documents related to collection, processing, drawing samples, transportation, and shipping. This information is necessary because it helps identify who performed what steps.

**Example(s):**

It is advantageous to keep employee signatures, initials, and dates of employment on a log for quick reference. This log would not need to include the entire record of employment.

In some CBBs, the human resources department may retain this information.

**STANDARD:**

*B2.5 The QM Plan shall include, or summarize and reference, a system for change control that includes at a minimum:*

*B2.5.1 A description of the proposed change and who is affected.*

*B2.5.2 Analysis of the change for compliance with these Standards and Applicable Law.*

*B2.5.3 Identification of risks of the change to the donor, CB unit, or recipient.*

*B2.5.4 Determination of impact on existing processes, policies, and Standard Operating Procedures.*

*B2.5.5 System for change approval, effective date, and implementation.*

*B2.5.6 Methods for communication of the change and training, if applicable.*

*B2.6 The QM Plan shall include, or summarize and reference, a system for document control. The document control system shall include the following elements at a minimum:*

- B2.6.1 Current listing of all critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:
  - B2.6.1.1 Policies and Standard Operating Procedures.*
  - B2.6.1.2 Worksheets.*
  - B2.6.1.3 Forms.*
  - B2.6.1.4 Labels.*
  - B2.6.1.5 Educational, promotional, and recruitment materials.**
- B2.6.2 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.*
- B2.6.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.*

**Explanation:**

This standard primarily addresses the need for a comprehensive document control system that covers all of the critical documents used by the CBB. The types of documents listed in the standard are what minimally have to be included in the document control system; however, CBBs should review their document management system to identify if other documents should also be included, such as work instructions and checklists.

There must be a listing of active critical documents. This list must include all critical documents that are currently in effect. Documents in electronic format should follow the described document control process of the CBB.

The document control system must include the assignment of a unique identifier for each individual document, a mechanism to identify the document version, and its effective dates of use. There must be processes for the creation, initial review/approval, and implementation/training of each document. The document control system should be designed to track document versions, and include a formal review and approval process for new documents and versions.

The CBB must have an SOP outlining methods by which the CBB creates, approves, implements, reviews, and updates its controlled documents. Controlled documents must include a system for numbering and titling that allows for unambiguous identification of the documents and revisions of documents with the same title. A system to approve new or changed documents that identifies the responsible individuals and clearly indicates the effective date must be in place.

**Evidence:**

The CBB must have a written document control procedure and change control policy with evidence that its elements are used for the documents currently active in the CBB.

**Example:**



Document identifiers and version identifiers may be present in the header or footer of controlled documents. An approval section may be part of the document (i.e., SOPs), or linked to the controlled document through its identifier (i.e., labels).

**STANDARD:**

- B2.6.4 A procedure for document distribution to relevant personnel, including written confirmation that relevant personnel have received and read the document.*
- B2.6.5 A system for document change control that includes description of the change, signature of approving individual(s), approval date, and effective date.*
  - B2.6.5.1 There shall be a system to ensure that controlled documents cannot undergo accidental or unauthorized modification.*
- B2.6.6 A system for document creation, assembly, review, storage, archival, retention, and retrieval.*
  - B2.6.6.1 There shall be a standardized system for denoting the date each document became effective and when it was archived, if applicable.*
  - B2.6.6.2 There shall be a system for the retraction of obsolete documents to prevent unintended use.*
  - B2.6.6.3 Records of archived Standard Operating Procedures, protocols, and labels, in their historical sequence including inclusive dates of use, shall be maintained indefinitely.*
- B2.6.7 A Standard Operating Procedure for preparation, approval, implementation, review, revision, and archival of all policies and Standard Operating Procedures.*

**Explanation:**

Rather than the implementation of a procedure being dependent on all staff reading and acknowledging the procedure, this standard should be interpreted to suggest that a task cannot be performed by personnel until they are trained. In other words, a policy can be implemented CBB-wide without all staff being trained. Minor revisions, such as grammatical and spelling modifications that do not warrant entirely new versions, may not require retraining of staff

The change control policy and/or procedure(s) must include at least the following elements: a method to control document changes that will prevent unintended modification and/or the use of obsolete documents; change proposal; review of proposed change; analysis of change for compliance with the Standards and Applicable Law; risk; and impact on existing processes, procedures and policies; approval of change; communication and/or training on the change as applicable; and implementation of the change. There must also be a documented system for the use, assembly, storage, archival, and retrieval of documents. Archiving is specifically mentioned in this standard and is an important element of the QM Program. If outcomes change over time, one needs to be able to go back to previous versions of policies, procedures, and forms to determine if an operational change is the cause.

**Evidence:**

The document control policy and/or procedure must meet these minimal criteria and there must be evidence that personnel follow the process. The inspector can confirm the effectiveness of the document control by tracking a controlled document (e.g., a form or SOP) from initial creation, through the proposal, approval, review and implementation of revisions and/or new versions, and archival. The written change control policy and/or procedure must be effective to prevent unintended changes to processes, policies, or procedures.

Signatures to indicate reading and/or training must be maintained for all new and revised SOPs. This is especially important in CBBs where the central facility manages separate CB Collection Sites. Electronic signatures may be acceptable so long as they can be produced for inspection. Information regarding electronic record systems can be found in B11.

The CBB must be able to show previous versions of a procedure that has been revised or replaced. Such “retired” procedures must be clearly marked in such a manner that they reflect the status of the procedure.

**Example(s):**

The document control process may be electronic or paper-based. Commercial document control software may be used to streamline this process. These systems can be configured to automatically ascribe a unique document identifier and version number. Initial approval and document receipt may be captured by electronic signatures. Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software to lock specific areas or the use of protected Portable Document Format (PDF). The intervals for periodic review may be set globally and automated reminders sent to relevant personnel via email. These systems can generally capture review date and outcome as well as requests for changes to documents.

**STANDARD:**

*B2.7 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures to support management of electronic record systems and electronic records and to maintain pertinent electronic records, if applicable.*

*B2.8 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event the CBB’s operations are interrupted.*

- B2.9 The QM Plan shall include, or summarize and reference, a system to maintain confidentiality.*
- B2.10 The QM Plan shall include, or summarize and reference, policies, Standard Operating Procedures, and a schedule for conducting audits of key CBB functions annually at a minimum to verify compliance with elements of the Quality Management Program and operational policies and procedures.*
- B2.10.1 Key functions shall include donor management, collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, and outcome analysis.*
- B2.10.2 There shall be a written procedure for the management of external audits and inspections.*
- B2.10.2.1 Documentation of results of inspection and accreditation visits shall be maintained indefinitely.*
- B2.10.3 Quality audits shall be conducted by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.*
- B2.10.4 Collection and analysis of data related to the audit shall be reviewed, reported, and documented, at a minimum, on an annual basis.*
- B2.10.5 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and determine the effectiveness of corrective and preventive actions when necessary.*
- B2.10.6 Audit results shall be shared with the appropriate Director and/or Medical Director, supervisor of the area audited, and other relevant staff.*
- B2.10.7 Audits shall include documentation that external facilities performing critical contracted services have met the requirements of the written agreements.*

**Explanation:**

An audit is a documented, independent inspection and review of an establishment's activities, performed according to procedures to verify the degree of compliance by examination of objective evidence. Audits should focus on key functions and may also be prompted in response to observed trends or occurrences (as well as designed to detect them). Audits should be scheduled on the basis of the importance of the activity to the quality of the product or service.

On-site audits of external facilities performing critical services to the CBB are not specified by these Standards but must be performed if they are required by Applicable Law.

**Evidence:**

CBBs shall provide evidence of a written audit schedule, audit results, actions taken, and follow-up assessments and audits. Review of audit schedules and results is intended to verify an

adequate audit process, but it is not the intent to use a facility's audits to identify deficiencies during an inspection.

**Example(s):**

On-site audits are required of CBBs holding a U.S. BLA for cord blood.

**STANDARD:**

*B2.11 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures to address errors, accidents, biological product deviations, adverse events, variances, and complaints, including the following activities at a minimum:*

**Explanation:**

For errors, accidents, biological product deviations, adverse events, variances, and complaints, the CBB must detect, investigate, document, track, evaluate, report, and correct the issues. Adverse events include severe adverse events during administration of the CB unit.

**STANDARD:**

*B2.11.1 Detection.*

*B2.11.1.1 There shall be a defined process improvement plan that includes policies or procedures for the recognition of all issues that require corrective action.*

*B2.11.2 Investigation.*

*B2.11.2.1 A thorough investigation shall be conducted by the CBB in collaboration with the CB Collection Site, CB Processing Facility, registry, and/or Clinical Program, as appropriate.*

*B2.11.3 Documentation.*

*B2.11.3.1 Cumulative files of errors, accidents, biological product deviations, adverse events, variances, and complaints shall be maintained.*

**Explanation:**

Details of errors, accidents, biological product deviations, adverse events, variances, and complaints must be compiled in a cumulative file to use for tracking and trending and be linked to the processing record.

The FACT definition of a complaint is "Any written, oral, or electronic communication about a problem associated with a distributed cord blood unit or with a service related to the collection, processing, storage, distribution, or infusion of a cord blood unit." It is important that there be documentation of investigation of all complaints. This is a reasonable approach to integrating patient safety into a quality plan.

**Example(s):**

A complaint file is specifically required by 21 CFR 1271 for U.S. CBBs.

**STANDARD:**

*B2.11.3.2 A written report of the investigation including conclusions, follow-up, and corrective action, if applicable, shall be prepared and maintained as part of the record for that final CB unit and maintained in the applicable cumulative file.*

*B2.11.3.3 Investigation reports shall be reviewed and signed by the CBB Director or designee.*

*B2.11.3.4 Records of all severe or unexpected adverse events or adverse reactions during CB collection and infusion shall be maintained.*

*B2.11.4 Tracking.*

*B2.11.4.1 Errors, accidents, biological product deviations, adverse events, variances, and complaints shall be tracked and trended in order to categorize and identify system problems and initiate corrective action.*

*B2.11.4.2 Investigation reports shall be utilized in quality monitoring and tracking in order to analyze trends.*

*B2.11.5 Evaluation.*

*B2.11.5.1 Planned deviations shall be pre-approved by the appropriate CBB Director and/or Medical Director, representatives from the QM Program, and other staff as appropriate.*

*B2.11.5.2 Unplanned deviations and associated corrective action, if necessary, shall be reviewed by the appropriate CBB Director and/or Medical Director, representatives from the QM Program, and other staff as appropriate.*

*B2.11.5.3 The CBB Director or designee shall review all errors, accidents, biological product deviations, adverse events, variances, and complaints in a timely manner. This review shall be documented.*

**Evidence:**

In all cases of errors, accidents, biological product deviations, adverse events, variances, and complaints, documentation must be linked to the CB unit record and be signed off by the CBB Director, and the information must be relayed to the appropriate individuals.

**Example(s):**

Some events are unexpected, such as the temperature in a refrigerator that stores reagents climbing slightly out of range, but may be qualified through minor testing or with quality control. Some events are expected, when one knowingly does not follow a procedural step. An example of the latter may be a CBB choosing to process an autologous donation that arrives outside of the time window described in the SOP due to an unavoidable delay in transport.

**STANDARD:**

*B2.11.5.4 Each complaint shall be evaluated to determine if the complaint is related to a product deviation or adverse reaction. Corrective action shall be initiated when appropriate.*

*B2.11.6 Reporting.*

*B2.11.6.1 When it is determined that the CB unit was responsible for an adverse reaction, the reaction and results of the investigation shall be reported to the Clinical Program, other facilities participating in the manufacturing of the CB unit, registries, and governmental agencies as required by Applicable Law or these Standards.*

**Explanation:**

In general, severe and/or unexpected events or reactions are required to be documented, including the investigation, conclusions, follow-up, and corrective action. Each CBB should define adverse events and reactions according to the regulations and standards pertaining to its location and activities.

If there is a reasonable possibility that the reaction may have been caused by the CB unit, the reaction and investigation results may need to be reported to governmental or grant agencies, IRBs, and/or registries as required by institutional requirements, law, or standards.

When reporting is required, there must be a mechanism to report in a timely fashion. The reaction and investigation also needs to be reported to other facilities taking part in the collection or processing. The results of the investigation must also be reported to the Clinical Program reporting the reaction.

It is recognized that CBBs are challenged in evaluating causality of adverse reactions as they can only be in as much control as the information provided to them by a Clinical Program. At the very least, during the investigation, CBBs can verify their own work, such as donor screening and testing, cell counts, sterility cultures, equipment and reagent quality control, reagent acceptability, labeling, clerical transcription, SOP deviations, and accuracy of calculations. Clinical Programs meeting FACT-JACIE Cellular Therapy Standards are required to notify CBBs of adverse reactions during administration and will be considered noncompliant with the FACT-JACIE Cellular Therapy Standards if it is not provided.

**Evidence:**

The CBB must make available to the inspector SOPs describing how adverse reactions are investigated and reported, files of adverse reactions, and evidence that adverse reactions are reviewed and signed by the CBB Director or designee and reported to the appropriate agencies, if necessary.

**Example(s):**

Internal communication of adverse reaction investigations and conclusions may occur in various formats. Written reports are always prepared and signed by the appropriate individuals, including the CBB Director or designee. These written reports, as well as tracking and trending, may be reviewed during a regularly scheduled QM meeting with inclusion in the meeting minutes. If applicable, results should be shared with other relevant staff.

CB units manufactured in the U.S. or intended for use in the U.S. are all regulated by the current Good Tissue Practices in 21 CFR 1271, but will also be subject to one of the following sets of regulations:

- Section 361 of the Public Health Services (PHS) Act (related CB units),
- Section 351 of the PHS Act (unrelated allogeneic CB units under IND), and/or
- 21 CFR Part 601 (minimally manipulated, unrelated CB units intended for hematopoietic reconstitution for specified indications under a biologics license application (BLA)).

The FDA published two guidance documents, one final, in October 2009 regarding minimally manipulated, unrelated allogeneic CB units. The final guidance discusses BLAs and the draft guidance discusses minimally manipulated, unrelated allogeneic CB units that do not meet licensing requirements. These documents can be found at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>.

In other countries, such as Australia, CB already is a licensed product and different governmental regulations apply.

CBBs listing their products in WMDA databases/registries must report serious adverse events to the Serious (Product) Events and Adverse Reactions (SPEAR), a WMDA-sponsored international centralized dataset of such events. SPEAR forms are located at <http://www.worldmarrow.org>.

Different agencies have different required timeframes for reporting adverse events. The FDA requirements are to report significant adverse events (SAEs) within 15 days of their occurrence, whereas CIBMTR reports must be submitted within 30 days. The CBB should have a proactive plan to acquire information regarding infusional SAEs.

**STANDARD:**

*B2.11.6.2 Errors, accidents, biological product deviations, variances, and complaints shall be reported to other facilities performing CBB functions on the affected CB unit and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees as necessary.*

**Explanation:**

Each CBB should define errors, accidents, biological product deviations, variances, and complaints, along with when and how each are reported. There must be a mechanism to report these events in a timely fashion to key individuals, including the CBB Director. The CBB is also expected to comply with institutional requirements and applicable governmental regulations

pertaining to reporting. Besides regulatory and accrediting agencies, there may also be registries, grant agencies, or IRBs that require notification in selected situations.

**Evidence:**

Files of errors, accidents, biological product deviations, variances, adverse events, and complaints must be available for inspector review. It is not the intent to use a CBB's adverse reactions, errors, accidents, biological product deviations, complaints, or variances to identify deficiencies during an inspection.

**STANDARD:**

*B2.11.7 Corrective action.*

*B2.11.7.1 Corrective action shall be implemented and documented as indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.*

*B2.11.7.2 Corrective actions shall include the initiation of retraining and/or re-education of employees and performing follow-up audits of deficiencies, as appropriate.*

*B2.11.7.3 Documentation of the corrective action shall include the nature of the problem requiring corrective action and the identity and disposition of the affected CB unit, if indicated.*

*B2.11.7.4 Documentation of the corrective action shall be maintained, including the dates of corrective action and a designated timeframe at which the outcome of the corrective action shall be evaluated.*

*B2.11.7.5 Corrective actions shall be evaluated by the appropriate Director and/or Medical Director, or designee, representatives from the QM Program, and other appropriate staff.*

**Explanation:**

Corrective action is usually initiated in response to internal or external audits, errors, accidents, biological product deviations, variances, adverse events, or complaints. A corrective action plan should be designed to further investigate or determine the root cause of the event or trend any possible effect on product quality. Any corrective action plan and follow up should be documented.

**Example(s):**

Corrective action plans may be initiated due to one specific event or for a series of events where an undesirable or unexpected trend is noted.

**STANDARD:**



B2.12 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical vendors, equipment, supplies, reagents, and facilities.

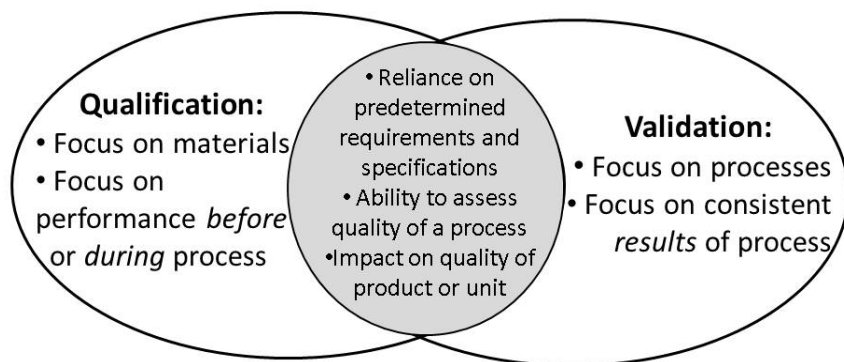
B2.12.1 Qualification studies shall be reviewed and approved by the CBB Director or designee from the QM Program.

B2.12.2 Suppliers of critical supplies, reagents, services, and equipment shall be qualified by a method that verifies they are compliant with applicable laws and regulations and these Standards.

**Explanation:**

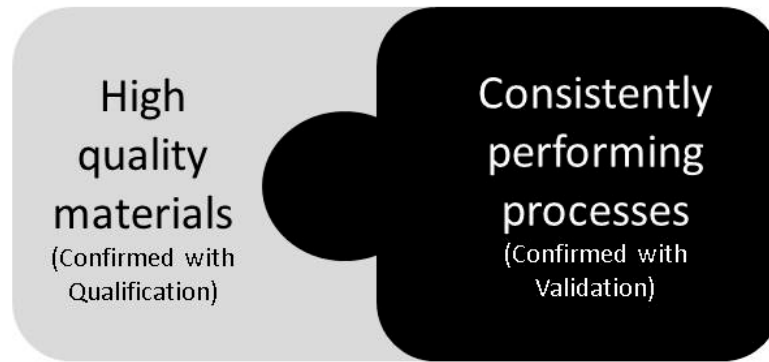
Qualification is defined as the establishment of confidence that equipment, supplies, and reagents function consistently within established limits. Sometimes qualification is confused with validation (required in B2.13), which is defined as confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. **Figure 2: Comparison and Contrast of Qualification and Validation** illustrates the differences and similarities between the two.

**Figure 2: Comparison and Contrast of Qualification and Validation**



While qualification and validation have two distinct objectives, they are often performed sequentially and/or at the same time. This is acceptable given the close relationship the two have on the quality of a process. **Figure 3: Interdependency of Qualification and Validation** illustrates how the two work together.

**Figure 3: Interdependency of Qualification and Validation**



- A procedure cannot be successful if inadequate materials are used
- Materials cannot perform as expected if used inappropriately during a procedure

The timing of qualification and validation can enable you to achieve synergies. When used in a sequential process, such as qualification before validation, it can help reduce duplicate efforts and streamline the assessment activities. When conducted concurrently, qualification and validation studies do not need separately allocated resources. This is especially true for performance qualification, which is when materials are qualified for their intended use. When used concurrently, performance qualification is simply a subset of the validation procedure.

There will be situations, though, when only one of the assessment activities is needed. This is true when you receive a new lot of a certain reagent that has already undergone performance qualification. It would need operational qualification to confirm its sterility and functionality, but would not require a new validation study.

The QM Plan must include a process to qualify equipment, supplies, and reagents to confirm their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical equipment, supplies, and reagents and must document that those standards are met before they are made available for use. Even if equipment, supplies, and reagents are qualified, the manner in which they are used (processes) must be validated to prevent product mix-ups, contamination, or cross-contamination.

All vendors providing equipment, supplies, and reagents must provide documentation indicating that their products are safe and perform to the standards required by the CBB, such as Certificates of Analysis or specification sheets. The CBB must evaluate and retain records of the specifications.

Equipment is qualified at installation (Installation Qualification (IQ)), usually by the manufacturer at set-up. Operational qualification (OQ) is performed by activities determining linearity, reproducibility, precision, and accuracy. Performance qualification (PQ) follows with calibration and quality control materials. Once IQ, OQ, and PQ are complete, validation of the procedure for which the equipment will be used is performed.

**Evidence:**

The CBB must provide the inspector the SOPs for qualification and validation. These should provide evidence of data collection, analysis, and evaluation, with follow-up of results. Specific qualification and validation studies must also be provided so that the inspector can verify the

appropriateness of the study design, conformance to applicable SOP(s), and oversight from the responsible parties.

**Example(s):**

For example, a new centrifuge is installed in a CB Processing Facility and the manufacturer performs IQ at set-up, leaving documentation of this activity with the facility. The facility would then perform speed, timer, and temperature checks as a means to accomplish OQ. Finally, the facility would test products for expected nucleated cell recovery and viability to verify that the centrifuge is capable of meeting the expected endpoints of the processing procedure, and thus PQ.

An example of a sequential validation is when the CBB creates a new procedure related to collection. The first step could be to qualify all the intended materials before embarking on a validation study. This way, the CBB can be confident that it is using the appropriate materials and any negative results of the subsequent validation study would not be due to inadequate or inappropriate materials.

In the U.S., manufacture of licensed CB units requires reagent lot identity testing.

**STANDARD:**

*B2.13 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation of critical procedures of the CBB functions.*

*B2.13.1 Determination of which critical procedures to be validated shall be made by the CBB Director or CBB Medical Director in collaboration with representatives of the QM Program.*

*B2.13.2 Each validation shall include:*

*B2.13.2.1 A validation plan, including conditions to be validated.*

*B2.13.2.2 Acceptance criteria.*

*B2.13.2.3 Data collection.*

*B2.13.2.4 Evaluation of data.*

*B2.13.2.5 Summary of results.*

*B2.13.2.6 Documentation of review and acceptance of the methodology by representatives of the QM Program.*

*B2.13.2.7 Review and approval by the CBB Director or designee of the validation results and conclusions.*

**Explanation:**

B2.13.2 specifies the minimum requirements for each individual validation study. Validations should be performed at the aggregate level for several CB units (enough to provide reasonable

assurances that the results could be applied to the entire inventory) rather than at the individual unit level. That is, the minimum number of samples used in validation studies will always be more than one.

**STANDARD:**

*B2.13.3 Changes to a process shall be verified or validated to ensure that they do not create an adverse impact anywhere in the operation.*

*B2.13.4 Records shall be maintained to document that procedures have been validated to achieve the expected end-points, including viability of CB cells and CB unit characteristics.*

**Explanation:**

Validation refers to confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation provides assurance that new or changed processes and procedures are capable of consistently meeting specified requirements. Process validation establishes that a process consistently produces a result or CB unit that meets its predetermined specifications and performs effectively with regard to its intended use.

Validations can be performed prospectively (prior to the implementation of a new or revised process), concurrently (at the same time that a process is being performed), or retrospectively (based upon accumulated production, testing, and control data). Validations should be performed on processes or the intended use of equipment, reagents, and supplies. Examples include new processing procedures and the use of reagents made on-site.

Validations must be designed to encompass key elements of the procedures, which are those parts of the process which impact cell viability and product integrity. Validations begin with the design of a validation protocol. The validation protocol consists of a written plan stating how a validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results. Validations should include worst-case scenarios, a set of conditions encompassing upper and lower processing limits and circumstances, including those within SOPs, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

These Standards allow for retrospective validation of established procedures. It is expected that formal re-validation occurs with major changes to a procedure, installation of new equipment, or observation of unexpected trends and variations. Validation of the training process may be evaluated by determination of a new employee's competence following the training.

**Evidence:**

SOPs for conducting validation and qualification, and example validation and qualification studies, must be available for inspector review. There should be a consistent mechanism for conducting the studies, analyzing the data, drawing conclusions, and documenting the implementation of changes resulting from the investigation. Reports of these activities should be complete, legible, and organized for review. A sampling of validation studies of the facility, processes, and uses of equipment, supplies, and reagents should be provided. The design of the study should be adequate to determine if the new or revised process achieves the purpose for which it is intended. The validation studies must include documented review by the CBB

Director or designee of the QM Program. The inspector will note poorly designed or inadequately performed validation studies during the review process.

**Example(s):**

Validation studies may be prioritized with the following criteria:

1. Focus on aspects for which failure to meet specifications could result in adverse event.
2. Conduct all specific studies required by the Standards.
3. Assess where your program or bank is at particular risk for nonconformance.
4. Supplement with audits.

**STANDARD:**

*B2.14 The QM Plan shall include, or summarize and reference, policies and procedures for CB unit tracking, tracing, and linkage that allow tracking from the infant donor to the recipient or final disposition and tracing from the recipient or final disposition to the infant donor.*

*B2.14.1 Linkage of the CB unit to the infant donor and mother shall be retained confidentially and indefinitely.*

**Explanation:**

While linkage must be maintained, the identity should not be readily apparent in the later stages of processing and storage. With the requirement to maintain long-term linkage with the CB donor, there is information collected and stored that could allow tracing of the CB donor by an interested third party. The CBB must demonstrate processes in its record system that prevents the unnecessary display of such demographic information.

**STANDARD:**

*B2.14.2 Documentation of all facilities involved in each stage of CB unit manufacturing shall be established and maintained.*

*B2.15 The QM Plan shall include, or summarize and reference, policies and procedures to trend, investigate, and evaluate details of clinical outcome data and CB unit characteristics.*

*B2.15.1 The CBB shall define expected clinical outcomes and CB unit characteristics.*

*B2.15.2 Both individual CB unit data and aggregate data shall be evaluated.*

**Explanation:**

The QM Plan must include, or summarize and reference, the CBB's process for tracking and evaluating clinical outcome data. CBBs are required to request certain types of data from Clinical Programs as outlined in E7.

**STANDARD:**

*B2.15.3 There shall be a written stability program that annually evaluates a minimum of three CB units.*

*B2.15.3.1 There shall be a plan for defining an expiration date.*

**Explanation:**

Because the length of CB unit storage is unknown, confidence needs to be demonstrated that the unit stored can provide acceptable hematopoietic reconstitution. Since units cannot easily be tested prior to release, the CBB must develop a stability program that annually tests units of various storage duration for viability and potency. Applicable Law may specify what testing and the frequency of testing that needs to be performed.

Processing methods change over time and may affect the expiration date. The stability program must test a reference sample from a CB unit from each method of processing used.

**Evidence:**

The inspector will review the stability program and the associated policies and procedures for identifying units to be tested and the acceptable end point parameters

**STANDARD:**

**B3**        *POLICIES AND STANDARD OPERATING PROCEDURES*

*B3.1        The CBB shall establish and maintain policies and/or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B2. These documents shall include all elements required by these Standards and shall address at a minimum:*

**Explanation:**

These Standards require that each CBB have written policies and SOPs that address all important aspects of the CBB. The CBB is not required to have an SOP titled for every item on the list, as long as each item is addressed within an SOP. The items in the checklist include the minimum requirements. In those circumstances where CBB or institutional standards vary from the minimal requirements, the CBB will be held to the higher standards.

To group similar topics together in a logical order, and to reduce redundancy, the Standards divide required policies and procedures into those intended to document the Quality Management (QM) Program (B2) and those intended to establish operational quality control (B3). Some required policies and procedures are included elsewhere in the Standards if believed to enhance better understanding of the requirements or if necessary to provide more detail.

A list of required policies and procedures in the NetCord-FACT Standards is in **Figure 4: Required Policies and Standard Operating Procedures**. The CBB should choose the most appropriate way to incorporate these topics into its QM Program. Unless specified otherwise, the Standards do not prescribe whether or not a topic must be in a policy, procedure, or both so long as the idea is addressed in writing in one of these quality documents. Furthermore, a dedicated policy or procedure is not required for each of these ideas; one or more of the required topics may be included in a single document.

While these topics are specifically required to be in an SOP, CBBs should be aware that additional policies and procedures may be necessary to obtain the appropriate process

approvals, train staff, facilitate consistency, and document compliance to the Standards. SOPs must comply with the NetCord-FACT Standards, and the table below should be used in conjunction with the Standards to verify that all required elements are included in the CBB's policies and procedures.

**Figure 4: Required Policies and Standard Operating Procedures**

<b>Subject</b>	<b>Standard</b>
Written Agreements	B2.3
Personnel Requirements	B2.4, B2.4.3.1, C3.3.12, C3.3.12.1, D3.1.7
Change Control	B2.5
Document Control	B2.6, B2.5.3, B2.5.4, B2.6.7
Electronic Record Systems	B2.7, B3.1.23, B11.8.2, B11.8.4
Interruption of Operations	B2.8
Audits	B2.10, B2.10.2
Errors, Accidents, Biological Product Deviations, Adverse Events, Variances, and Complaints	B2.11, B2.11.1.1
Qualification	B2.12
Validation	B2.13
Tracking, Tracing, and Linkage	B2.14, C3.3.7
Outcome Data and Cord Blood (CB) Unit Characteristics	B2.15, B3.1.22, E7.2
Donor Recruitment	B3.1.1, C3.3.1
Maternal Screening and Testing	B3.1.2, C3.3.2
Informed Consent	B3.1.3, C3.3.3
Donor Eligibility Criteria and Determination	B3.1.4, C3.3.4
Interaction Between the CB Collection Site and the CBB	B3.1.5
Infant donor health	B3.1.6, C3.3.5, C3.3.6
Collector training	B3.1.7, C3.3.12, C3.3.12.1
Collection of CB units, associated samples, and maternal samples	B3.1.8, C3.3.8, C6.3
Completion of records at the CB Collection Site	B3.1.9
Storage of CB units, associated samples, maternal samples, and documentation at the CB Collection Site	B3.1.10, C3.3.10, C6.7
Transport and shipping of the CB unit, associated samples, maternal samples, and documentation to the CB Processing Facility	B3.1.11, C3.3.11
Labeling of the CB unit, associated samples, reference samples, retention samples, maternal samples, and associated documents at the CB Collection Site and CB Processing Facility	B3.1.12, C3.3.9, C6.5, D3.1.2
CB unit acceptance criteria for receipt, processing, cryopreservation, and storage	B3.1.13, C5.3.5, D3.1.1, D3.1.6, D4.2.4, D4.2.4.2, D6.1, D6.2, D7.3, D7.4
Process control, including product	B3.1.14, D9.2.1, D9.2.2, D9.2.3

specifications and nonconforming products	
Storage of reference samples, retention samples, and maternal samples for testing	B3.1.15, D3.1.3
Communicable disease testing, microbial cultures, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.	B3.1.16, D3.1.4
Notification of mothers or their responsible physicians and/or governmental agencies, when required, of positive or indeterminate communicable disease and/or genetic test results	B3.1.17
Listing, search, selection, reservation, release, and distribution of CB units	B3.1.18, B3.1.20, D3.1.6, D11.4, E1.3.1, E1.6, E2.1, E5.1, E5.4
HLA typing	B3.1.21, E1.3.2, E1.3.3
Data management	B3.1.24
CB unit records	B3.1.25
CB unit disposition	B3.1.26, D3.1.10, D9.1, D9.3.1
Facility management and environmental monitoring	B3.1.27, C3.3.15, D3.1.8
Materials management, maintenance and monitoring of equipment, cleaning and sanitation procedures, and disposal of medical and biohazardous waste	B3.1.28, B7.6.3, C3.3.13, C3.3.14, C3.3.15, D3.1.8
Emergency and safety procedures	B3.1.29, D1.9.1
Biological, chemical, and, if applicable, radiation safety	B3.1.30, B4.2, D1.9.3
Disaster plan, including CBB-specific issues	B3.1.31, D3.1.9
Confidentiality	B5.8.2, B10.4
Inventory management	B9.5, B10.1.1

**Example(s):**

The policies and SOPs can be generated within the CBB or in collaboration with other institutional infrastructures. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and emergency response. In cases where general policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the CBB, the facility must develop its own policies and SOPs. In situations where institutional policies and procedures are utilized, there must be a defined mechanism within the CBB for initial review, review every two years, and approval of revisions.

**STANDARD:**

*B3.1.1 Donor recruitment.*

**Explanation:**

Donor recruitment policies must describe how a CBB informs potential participants or customers of their service and potential participation. SOPs must also delineate donor acceptance criteria. This standard does not imply that marketing strategies are revealed in policies and SOPs, but that recruitment policies adequately instruct personnel to properly perform these duties.



**Example(s):**

A uniform Donor Questionnaire is on the FACT website at [www.factwebsite.org](http://www.factwebsite.org) > Standards and Resources > Resources that was developed to screen donors of products other than CB for communicable disease risk. While the questionnaire does not satisfy all screening requirements for CB donors, CBBs can use the questionnaire for the communicable disease screening. Registries also may have examples of donor questionnaires for CB maternal donors.

**STANDARD:**

- B3.1.2 Maternal screening and testing (including interpretation and acceptable results).*
- B3.1.3 Informed consent.*
- B3.1.4 Donor eligibility criteria and determination.*
- B3.1.5 Interaction between the CB Collection Site and the CBB.*
- B3.1.6 Documentation of infant donor health at birth.*
- B3.1.7 Collector training.*
- B3.1.8 Collection of CB units, associated samples, and maternal samples.*
- B3.1.9 Completion of records at the CB Collection Site.*
- B3.1.10 Storage of CB units, associated samples, maternal samples, and documentation at the CB Collection Site.*

**Explanation:**

Validation data should prove that the storage conditions do not affect the quality of the CB unit. If storage of units and/or samples is to be at room temperature at a given time, the acceptable temperature range of room temperature must be defined.

**Example(s):**

In the U.S., the FDA indicates liquid CB units are stored at 15-25°C.

**STANDARD:**

- B3.1.11 Transport and shipping of the CB unit, associated samples, maternal samples, and documentation to the CB Processing Facility.*

**Explanation:**

Defined temperature ranges for transport and shipping must be included in the procedures.

**STANDARD:**

*B3.1.12 Labeling of the CB unit, associated samples, reference samples, retention samples, maternal samples, and associated documents at the CB Collection Site, at the CB Processing Facility, and at release for administration.*

**Explanation:**

Procedures for labeling the unit and reference samples must include measures to prevent sample mix-ups.

**Example(s):**

An example method for preventing sample mix-ups in the CB Processing Facility is to only process one CB unit under the biological safety cabinet at a time.

**STANDARD:**

*B3.1.13 CB unit acceptance criteria for receipt, processing, cryopreservation, and storage.*

*B3.1.14 Process control, including product specifications and nonconforming products.*

*B3.1.15 Storage of reference samples, retention samples, and maternal samples for testing.*

*B3.1.16 Communicable disease testing, microbial cultures, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.*

*B3.1.17 Notification of mothers or their responsible physicians and/or governmental agencies, when required, of positive or indeterminate communicable disease and/or genetic test results.*

**Explanation:**

Maternal samples must be drawn within seven days before or after delivery to reflect their infectious status at the time of donation. Retesting donors at six months is not practical in most CB banking settings. Therefore, interpretation of indeterminate or repeatedly reactive test results cannot be concluded by the CBB. Since the risk of transmission remains, abnormal results are communicated to the mother and/or physician so that appropriate follow-up can occur in light of the donor's clinical presentation and history.

The rationale for reporting indeterminate or unconfirmed reactive screening results is to alert physicians and mothers of potential health-related issues. It is the CBB's responsibility to define who actually contacts the mother.

**Example(s):**

There may be regulations that require the CBB to report certain results to agencies, such as the state department of health.

**STANDARD:**

*B3.1.18 Criteria for qualification and listing of CB units available for search and administration.*

**Explanation:**

Individual CBBs must develop their own release criteria, ensuring accuracy/relevance of testing methods and recovery of viable progenitor cells, and follow them accordingly.

**Example(s):**

Examples of qualification parameters designed in the U.S. include, for example, those developed by the NMDP Quality Standards committee and the Health Resources and Services Administration (HRSA) solicitation, which were designed with input from transplant physicians to reflect nationally accepted standards and for financial viability. Table 2 in the FDA guidance, “Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications,” also includes qualification parameters for licensure. While these parameters were developed for use in the U.S. and for CB units imported to the U.S., they may be applicable in other countries as well.

**STANDARD:**

*B3.1.19 Listing, search, selection, reservation, release, and distribution of CB units.*

*B3.1.20 HLA typing to include requirements for resolution, loci, timing, and verification.*

**Explanation:**

Two tests are required for HLA typing, one performed at the time of banking and one performed on the attached segment after the unit has been frozen and stored. All verification typing of CB units should be reviewed and verified against the original typing as a means to confirm unit identity. Discrepancies must be resolved before a unit can be released.

**Example(s):**

The confirmatory HLA typing may be performed by a laboratory other than that used by the CBB for initial typing, such as the potential Clinical Program or a central laboratory designated by a registry.

**STANDARD:**

*B3.1.21 Verification that the infant donor and recipient are different individuals in the case of complete HLA matches.*

**Explanation:**

This standard is in place to prevent the use of an autologous unit when the intended purpose is an allogeneic transplant. Donor families may forget that they donated CB and the Clinical Program is blinded to the identity of the donor.

**Example(s):**

One approach to ensuring that they are not the same is for the Clinical Program to verify that donor and recipient date of birth are not the same or supply adequate information to the CBB, such as recipient date of birth, so that the verification can take place there.

**STANDARD:**

*B3.1.22 Collection and analysis of transplant outcome data.*

*B3.1.23 Electronic record entry, verification, and revision.*

*B3.1.24 Data management.*

*B3.1.25 CB unit records.*

*B3.1.26 CB unit disposition.*

**Example(s):**

The disposition of a CB unit could, for example, be stored, discarded, released for administration, administered, designated for research, etc.

**STANDARD:**

*B3.1.27 Facility management and environmental monitoring.*

*B3.1.28 Materials management, maintenance and monitoring of equipment, cleaning and sanitation procedures, and disposal of medical and biohazardous waste.*

**Explanation:**

Environmental monitoring may be necessary to verify that cleaning and sanitation procedures are effective and prevent CB unit contamination or cross-contamination. For CB Processing Facilities, see D1 for more details.

**STANDARD:**

*B3.1.29 Emergency and safety procedures.*

*B3.1.30 Biological, chemical, and, if applicable, radiation safety.*

**Explanation:**

Details regarding what is required for this standard can be found in B4.2.

**STANDARD:**

*B3.1.31 Disaster plan, including CBB-specific issues.*

**Explanation:**

A method to describe how a CBB deals with the scope of possible events that constitute real threats to the personnel and inventory must be prescribed. It should identify internal disasters (such as loss of vacuum in a liquid nitrogen tank) and external disasters (such as loss of power in a building structure in severe weather or other natural event). These disaster plans will vary based on regional issues but must address how the CBB will continue its core operations in the event of a disaster.

**Example(s):**

Many facility management policies and SOPs are maintained at the institutional level, which is acceptable. However, the CBB must address CB banking-specific issues. This may include specific procedures for maintenance and monitoring of equipment not used elsewhere or not covered in the institution's overall procedures, or specific procedures for how to handle a CB unit in the middle of processing in the event of a disaster.

The disaster plan may distinguish steps to take for minimal disasters in addition to major disasters. They may also include a business contingency plan.

**STANDARD:**

*B3.2 The CBB shall maintain a detailed Standard Operating Procedures Manual. The Standard Operating Procedures Manual shall include at a minimum:*

**Explanation:**

Typically, the SOP Manual is maintained separately from the actual QM Plan, but it must still comply with the QM Plan's requirements, such as document control. A written copy or electronic version (with provision of hardcopy as necessary) of the CBB's policies and SOP Manual (including Work Instructions at CBBs following ISO 9000) must be immediately available to all relevant employees in their working environment. Any copies of the policies and SOP manual must be identical to the source document and those copies must not be used to alter, modify, extend, delete, or otherwise edit any SOP. Only current SOPs shall be available to the staff performing the work. SOPs that have been retired shall be accessible for reference as needed for audits or other quality control purposes.

**Evidence:**

The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector will expect to see the SOP Manual or electronic access to SOPs in all performance areas of the CBB. The SOPs should be organized in such a manner for the inspector to ascertain that the SOPs are comprehensive, defining all aspects of the CBB. The orders, worksheets, reports, labels, and forms must be part of each SOP. The purpose of this standard is to assure that not only are these documents easily accessible to a reader of the SOP but also provide guidance as to how they should be used.

There will not be time to read all policies and SOPs during the on-site inspection. The inspector is provided a Table of Contents for the SOP Manual with the pre-inspection material. The Table of Contents is examined for evidence of SOPs addressing each item before arriving at the inspection site. Prior confirmation that a specific SOP has been generated reserves limited on-site inspection time for activities that can only be verified in person at the inspection site, such as observing that a practice is aligned with its policy or SOP.

**STANDARD:**

*B3.2.1 A table of contents.*

*B3.2.2 A standardized format for policies, procedures, worksheets, forms, and labels.*

*B3.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual Standard Operating Procedure shall include:*

*B3.3.1 A clearly written description of the objectives.*

*B3.3.2 The personnel responsible for its execution.*

*B3.3.3 A description of the facility, equipment, and supplies required.*

*B3.3.4 A stepwise description of the procedure.*

*B3.3.5 Acceptable end-points and the expected range of results, if applicable.*

*B3.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.*

*B3.3.7 A reference section listing appropriate literature, if applicable.*

**Explanation:**

There must be an SOP outlining the method by which the CBB creates, reviews, and updates its SOPs (the so-called “SOP for SOPs”). Standardization of SOPs should include a system for numbering and titling that allows for unambiguous identification of procedures. The CBB should be consistent in the design of reports, worksheets, and forms. The policies and SOPs must be detailed, be unambiguous, and adequately define all operational aspects of the CBB.

**Evidence:**

All elements of an SOP must be present as defined in the “SOP for SOPs,” and there must be consistency in format from one SOP to another. The language in the SOP should be clear and allow an appropriately trained individual to achieve the goals of the procedure.

The procedure for the development, approval, implementation, revision, and archiving of SOPs must be available for inspector review.

There will not be time to read all policies and SOPs during the on-site inspection. The inspector is provided a Table of Contents for the SOP Manual with the pre-inspection material. The Table of Contents is examined for evidence of SOPs addressing each item before arriving at the inspection site. Prior confirmation that a specific SOP has been generated reserves limited on-site inspection time for activities that can only be verified in person at the inspection site, such as observing that a practice is aligned with its policy or SOP.

**Example(s):**

Though not required, the inclusion of diagrams and tables within policies and SOPs may be helpful to facilitate understanding of the procedure.

How orders, worksheets, reports, labels, and forms are included as part of an SOP can be done in different ways. For example, they may be included within the SOP itself or referenced in the SOP as a separately controlled document. However this is done, the worksheets, reports, labels, and forms must be under document control.

**STANDARD:**

- B3.3.8 A current version of worksheets, forms, reports, and labels, where applicable.*
- B3.3.9 The date(s) and the approval signature of the CBB Director, the QM Supervisor, and relevant key personnel prior to implementation.*
- B3.3.10 The date of review or revision and the approval signature of the CBB Director or designee, the QM Supervisor, and relevant key personnel upon procedural modifications and at least every two years after implementation.*

**Explanation:**

Although the Standards indicate that an individual designated by the CBB Director may review procedures every two years, the CBB Director remains ultimately responsible for this process. The designated individual must be knowledgeable, by virtue of education or training, of the subject matter being discussed in the SOPs.

The review of SOPs, policies, and worksheets every two years is intended to confirm that the documents accurately reflect practices. Whenever a change in practice is introduced the relevant controlled documents must be implemented or revised before the change is put into effect.

**Evidence:**

A review of the SOP manual should demonstrate that, in addition to the review every two years, revisions are made throughout the year in conjunction with changes in practices.

**STANDARD:**

- B3.4 All policies and Standard Operating Procedures shall comply with these Standards.*
- B3.5 Copies of policies and Standard Operating Procedures of the CBB relevant to the processes being performed shall be readily available to the CBB personnel.*
- B3.6 All personnel at the CBB, CB Collection Sites, and CB Processing Facilities shall follow the applicable policies and Standard Operating Procedures established by the CBB.*
- B3.7 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.*

**Evidence:**

It is expected that a correlation between process and SOPs can be observed. Personnel shall demonstrate an understanding that they are required to follow relevant SOPs.

**Example(s):**

Responsibilities for following SOPs may be an element of training and/or personnel may be assessed for competency in the performance of procedures relevant to their duties.

**STANDARD:**

**B4 FACILITIES AND SAFETY**

- B4.1 All CBB facilities and sites shall be safe, sanitary, and secure.*
  - B4.1.1 The CBB space shall be of adequate size, construction, and location to maintain safe operations, prevent contamination, and ensure orderly handling.*
  - B4.1.2 The CBB space shall be maintained in a clean, sanitary, and orderly manner to prevent introduction, transmission, or spread of communicable disease.*
  - B4.1.3 Separate areas shall be identified and maintained for processing and storage of CB units to prevent mislabeling, mix-ups, contamination, and cross-contamination of CB units.*
  - B4.1.4 The CBB shall be secure to prevent the admittance of unauthorized individuals.*
- B4.2 There shall be policies and Standard Operating Procedures for biological, chemical, and radiation safety as appropriate, including:*
  - B4.2.1 Communicable disease agents.*
  - B4.2.2 Chemical hygiene.*
  - B4.2.3 Hand washing.*
  - B4.2.4 Fire safety.*
  - B4.2.5 Radiation safety, if applicable.*
  - B4.2.6 Latex allergy.*
  - B4.2.7 Power failures.*
  - B4.2.8 Liquid nitrogen.*
  - B4.2.9 Discard of biological waste.*

**Explanation:**

This standard applies to all facilities involved in CB collection, banking, and release for administration. Compliance with applicable local and/or regional safety regulations should be addressed by the CBB.



The CBB must identify the parameters that should be controlled and monitored based on their potential effect on product quality. Environmental considerations for processing steps should include temperature and may include humidity control, ventilation and air filtration, and disinfection of the room and equipment at appropriate time intervals. Environmental monitors for controlled space should include measures of air quality such as particle counts and microbial colony counts to minimize airborne contaminants. There must be ongoing monitoring of any parameters that have been determined to be critical and these should be defined by an SOP and compliance should be evident through quality records.

Cleaning and sanitation of CBB facilities must be performed on a regular basis in order to prevent contamination and cross-contamination of CB. The methods used must be specified by an SOP. While the bench-top, biological safety cabinet, and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces that may be cleaned by outside service agents, such as floors, walls, and ceilings, also fall under this standard. The CBB, together with the cleaning services provider, must establish SOPs for this activity. These SOPs must assign responsibility for who performs the sanitation procedures, the methods used, and the schedule.

Policies and SOPs must document consistency with good biosafety procedures, including adherence to universal precautions and to federal, state, or provincial regulations regarding safety.

All persons who may be exposed to blood must have appropriate personal protective equipment available to them. The type of exposure that may be encountered will determine the appropriate protection. If aerosol exposure is likely, masks, goggles, and gowns or aprons should be provided. Gloves must be provided whenever potential exposure exists and when sterile procedures are required to protect the CB unit and/or personnel. There must be written instructions for action to be taken in case of exposure to communicable disease agents.

Where relevant, there must clearly be demonstrated policies and procedures for safe use of liquid nitrogen, chemicals, and radioactive material, including instructions for spillage and contamination. Any potentially biohazardous material shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste.

**Evidence:**

During the inspection, the inspector will observe personnel for use of protective clothing and other biosafety precautions. Employee's personnel files must document compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. The inspector will also examine how CB and other biological samples are being handled and discarded and compare his/her observations with the written protocols. The presence of unused equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents and supplies may also contribute to an unsafe environment.

**Example(s):**

The CB Processing Facility may not require a classified environment provided that the processing steps requiring exposure to the environment are performed in a biological safety cabinet. However, a facility that extensively manipulates CB and performs procedures with many “open” steps may require a greater level of environmental control. Local or regional guidelines may have more specific requirements such as adherence to the principles of Good Manufacturing Practice (GMP). Contaminants in the CB Processing Facility can be minimized through air filtration and by ensuring that the air pressure within the facility is positive to the surrounding area (room pressure monitors should be used).

Specific safety procedures may be maintained within a designated Safety Manual or may be incorporated into the relevant SOPs. Safety training, including universal precautions (“standard” precautions per the U.S. Centers for Disease Control) for handling blood is a requirement of the Occupational Safety and Health Administration in the U.S., and equivalent regulations apply in other countries.

**STANDARD:**

**B5**            **CORD BLOOD BANK OPERATIONS**

*B5.1            The responsibilities of each CB Collection Site, CB Processing Facility, collecting health care professional, and registry as they relate to the CBB shall be clearly defined and documented.*

*B5.1.1        A CBB that includes multiple CB Collection Sites and/or CB Processing Facilities shall employ coordinated policies and Standard Operating Procedures, protocols, staff training and competency evaluation procedures, and quality management systems.*

*B5.1.2        A CBB that includes multiple CB Collection Sites and/or CB Processing Facilities shall demonstrate evidence of regular interaction between these CB Collection Sites and/or CB Processing Facilities and the CBB.*

**Explanation:**

There are many organizational approaches used by Cord Blood Banks (CBB) with varying centralization of process control by the CBB itself. The CBB will need to describe its approach to training, supplies management, and performance evaluation, and demonstrate interactions between the CBB and CB Collection Sites that are commensurate with the degree of autonomy of the sites. Agreements with CB Collection Sites define the extent of their responsibility and are signed by authorized parties from both. Processes outside of the responsibility of the particular relationship need not be included in an agreement with the facility.

CBBs that operate CB Processing Facilities in different locations will need to describe the relationship/interaction between the external CB Processing Facilities and the CBB, including management of training; transport between sites; supplies management; storage of records and samples; and processes for making CB units available for search, release, and distribution.

In the unrelated donor setting, there are often choices as to the search registry on which a CB unit can be listed. The organizational chart should show the local donor registry and all of the international donor registry(ies) on which its CB units are listed for searching. This is important for obtaining an understanding of where the CB unit information is being disseminated.

The CB unit is the end-product of a series of processes: collection, screening, testing, processing, and storage. It is not possible to evaluate a CB unit in isolation of the screening and collection. In the unrelated donor setting, there are more stringent requirements in the initial donor screening and collection procedures. This may be the only opportunity to elicit family infectious disease risk and genetic screening information given limited follow-up ability post collection. Additionally, the privacy and donor safety requirements are essential to protecting the rights and wellbeing of the infant and maternal donor. The CBB must either manage the scope of activities related to the collection of CB at the CB Collection Site or have a very close working relationship with the CB Collection Site. The CBB must ensure that the collection procedures are compliant with these Standards and that the collection process is monitored by its QM program.

Application of this standard to collections performed in non-fixed CB Collection Sites may be challenging. In practice, a CBB using a non-fixed site has a standard collection practice that is communicated to the collection staff in multiple ways - letters directly to licensed health care providers when they assume responsibility for collecting a CB unit, instruction sheets in each collection kit directed to the collector, and on-going interaction between the collection staff and the CBB's Customer Service staff who provide support from the time of enrollment through the transport or shipping of the CB unit to the CB Processing Facility. For related collections at non-fixed sites, the business relationship is between the family and the CBB, not directly between the CB Collection Site and CBB; therefore, the opportunity for documentation of training and competency at the CB Collection Site is limited.

Whether related or unrelated, a CBB must facilitate the collection of the CB unit. Real or perceived undue burden on the CB Collection Site would reduce participation in the process and thereby reduce the opportunity for the CBB to meet the goals of diversity and total numbers. With appropriate training of the collecting health care professional, he/she can perform high quality collections.

**Example(s):**

To document responsibilities of a CB Collection Site, collection technique, labeling, and transportation should be discussed in the agreement with the site. Testing, banking, storing, and distribution for administration are not required to be discussed if the site is not responsible for these tasks.

**STANDARD:**

*B5.2 The CBB shall be responsible for all components of CB unit manufacturing, including at a minimum:*

*B5.2.1 Donor recruitment and consent processes.*

*B5.2.2 Infant donor and maternal screening and testing.*

*B5.2.3 Donor eligibility determination.*

- B5.2.4 Documentation of infant donor health at birth.*
- B5.2.5 Collection.*
- B5.2.6 Testing.*
- B5.2.7 Processing.*
- B5.2.8 Labeling.*
- B5.2.9 Cryopreservation.*
- B5.2.10 Storage.*
- B5.2.11 Release for listing.*
- B5.2.12 Listing CB units available for search.*
- B5.2.13 Selection and reservation.*
- B5.2.14 Release of the CB unit for administration.*
- B5.2.15 Transportation and shipping.*
- B5.2.16 CB unit records.*
- B5.2.17 CB unit disposition*
- B5.2.18 Recipient follow-up and outcome analysis.*

**Example(s):**

According to the FDA, manufacture of a CB unit ends after the unit has been distributed from the CBB. However, the CBB is still responsible for working with the Clinical Program to obtain information regarding administration of the CB unit for quality purposes.

**STANDARD:**

- B5.3 Records of each CB unit shall be made concurrently with each stage of donor management and CB unit collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, distribution, and/or disposal in such a way that all steps may be accurately traced.*
- B5.3.1 Records shall identify the person immediately responsible for each step from collection to final disposition of the CB unit and include appropriate dates and times to provide a complete history of the work performed and to relate the records to a particular CB unit.*

**Explanation:**

CBBs must be able to track and trace the CB unit from collection to final disposition. CBBs may not have immediate access to information regarding who administered the CB unit, but it should attempt to obtain information from the Clinical Program regarding if the CB unit was administered. Some of this information may be difficult to obtain, and it is recognized that CBBs are limited by what information Clinical Programs provide. The CBB does, however, need to make a reasonable attempt to obtain the information. These efforts must be documented.

**STANDARD:**

- B5.3.2 Records shall be as detailed as necessary for a clear understanding by a person experienced in CBB procedures.*
- B5.4 The CBB shall have an established relationship with each fixed CB Collection Site to ensure implementation of and compliance with the CBB QM Program and Standard Operating Procedures.*

**Explanation:**

For collections at fixed sites, there must be a written agreement between the CB Collection Site and the CBB.

**STANDARD:**

- B5.5 The CBB shall incorporate CB collection activities at fixed and nonfixed CB Collection Sites into its Quality Management program.*
- B5.6 The CBB shall utilize an HLA testing laboratory appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), the European Federation for Immunogenetics (EFI), or equivalent accrediting organization outside North America and Europe, with the capability of carrying out deoxyribonucleic acid (DNA)-based HLA typing.*

**Explanation:**

ASHI and EFI are the recognized authorities in histocompatibility. The laboratory results upon which donor selection for an allogeneic transplant is made must meet these stringent requirements.

**Evidence:**

Documentation required is a copy of the current (in-date) ASHI, EFI, or equivalent accrediting organization accreditation certificate for the laboratory.

**STANDARD:**

- B5.7 All laboratories utilized by the CBB for testing of reference samples and maternal samples shall be accredited, certified, or licensed to perform such testing in accordance with Applicable Law.*
- B5.7.1 The CBB shall maintain documentation of the accreditation, certification, or licensure of these laboratories to perform this testing.*

*B5.7.2 When external laboratories are used for any aspect of reference sample or maternal sample testing, the CBB shall maintain a record of all samples sent to such laboratories, including the identifiers, results, date sent, and date results are received.*

**Explanation:**

CBBs shall maintain current accreditation, certification, or licensing documentation of the laboratories selected to perform testing. CBBs should retain information regarding the name and version of the assays used in performing testing. This information does not need to appear on the label, but should be available if needed.

**STANDARD:**

*B5.8 Confidentiality.*

*B5.8.1 There shall be a process for maintenance of confidentiality of all records and communications among the CBB, the CB Collection Sites, the CB Processing Facility, testing laboratories, registries, and Clinical Programs according to Applicable Law.*

*B5.8.2 The CBB shall have written policies and Standard Operating Procedures for circumstances where the infant donor's mother or legal guardian and/or her physician could be contacted.*

*B5.8.3 Employee records shall be maintained in a confidential manner as required by Applicable Law.*

**Explanation:**

The CBB should request that the Clinical Program not reveal confidential information such as the time and date of collection to the recipient, the recipient's family, or representatives of the clinical personnel. While transplant coordinators and laboratories require details to select donors and confirm product identity, Clinical Programs should respect the confidentiality of donors and limit the communication of information that could potentially identify the donor. Recipient families will naturally be curious about the donor and the source providing the CB unit, but, for example, the combination of CBB and date of birth could provide the recipient with information adequate to trace the donor. It is the role of the CBB and the listing registry to educate the Clinical Programs about potential breaches of confidentiality.

**STANDARD:**

*B5.9 Quality control procedures shall be developed to monitor the continuing adequacy of the procedures, reagents, equipment, and supplies as used under routine operating conditions by the CBB personnel.*

*B5.9.1 The results of ongoing internal monitoring shall be documented and checked, and trends shall be analyzed on a regular basis.*

**Explanation:**

Monitoring is similar to auditing but represents a more regular check of the same routine indicators. Both audits and monitors are conducted to assure that the QM Program is operating effectively and to identify trends and recurring problems. Both are designed to result in improved processes and outcomes. Both can focus on broad processes or very specific components of a process.

Results of monitors and audits can indicate the need for further action, corrective and/or preventive. The frequency for data collection and analysis of monitoring should be established in accordance with the QM Plan. Some indicators may be reported concurrently with each occurrence while others may be retrospectively analyzed and reported at defined intervals. Once collected, the data should be analyzed and assessed for improvement opportunities. Strategies for improvement should be identified and implemented. The results of the implemented strategies should be measured and the improvement strategies either continued or new alternatives developed depending on the results.

**Evidence:**

There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

**Example(s):**

Examples of elements to be monitored include cell recovery, viability, and bacterial contamination. A CBB might monitor the number of CB units that do not meet minimum volume criteria to assess a collector's performance. A CB Processing Facility may track its average nucleated cell recovery and viability from month to month to demonstrate that the process is in control or to detect a trend. In the same way, a CB Processing Facility could track its bacterial contamination rates which could lead to an investigation of collection techniques, processing method, or environmental conditions.

**STANDARD:**

*B5.10 There shall be a process for the regular review of records and for the assessment of record review to identify recurring problems, potential points of failure, or need for process improvement.*

**Explanation:**

Reviews need to include both evaluation of aggregate data and reviews of individual records. Common control points are the time of transfer from quarantine to long-term storage or at time of listing the CB unit on registries. Documented review of the donor screening and testing, collection procedure, processing, freezing curve, warming events, and/or post freeze testing are examples of key steps that need to be reviewed.

**STANDARD:**

*B5.11 The CBB shall obtain, maintain, and analyze sufficient critical outcome data to ensure that the procedures in use in the CBB consistently provide a safe and effective product.*

**Explanation:**

The CBB must maintain the outcome data outlined in E7 at a minimum. While it is understood that a CBB is not in control of a Clinical Program's responsiveness in providing outcome data, the CBB should make it clear in an agreement with the Clinical Program that it is required to obtain this information for analysis of quality, safety, and efficacy and demonstrate diligence in obtaining a high percentage of at least Day 100 and one-year outcome data.

**Example(s):**

Outcome data provides valuable information necessary for evaluating the quality of a CB unit. For example, if an infusion reaction occurs, a CBB would want to use that data to investigate if their processes contributed to the event. A Clinical Program's thawing results compared to the CBB's own thawing results may shed light on the safety of the CB unit during transportation or shipping.

**STANDARD:**

*B5.12 Institutional Review Board or Ethics Committee Requirements.*

*B5.12.1 In compliance with Applicable Law, the CBB shall have formal review of investigational protocols and maternal consent for CB banking and related activities by a mechanism that is approved by appropriate governmental authority.*

*B5.12.2 The CBB shall maintain documentation of all its research protocols, Institutional Review Board or Ethics Committee approvals or equivalent, correspondence with regulatory agencies, investigational new drug or device exemptions, annual reports, and any adverse events.*

**Example(s):**

In the U.S., the appropriate governmental authorities are the Office of Human Research Protections under the Department of Health and Human Services (HHS) and/or the FDA. Minimally manipulated CB units that are intended for related use only, such as those collected and stored in directed banking programs, are regulated solely under the authority of section 361 of the PHS Act (21 CFR 1271) and are not subject to IRB/IND or licensing requirements. CBBs with minimally manipulated, unrelated allogeneic CB units are subject to IRB, IND, or BLA requirements.

In the UK, the appropriate governmental authority is the Human Tissue Authority. In Australia, the appropriate governmental authority is the Therapeutic Goods Administration.

**STANDARD:**

**B6 CODING AND LABELING OF CORD BLOOD UNITS**

*B6.1 ISBT 128 Coding and Labeling.*

*B6.1.1 CB units shall be identified according to the proper name of the unit, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.*



**Explanation:**

This required terminology is *ISBT 128*, the international information standard for transfusion and transplantation. This standard terminology has been used in the Circular of Information (COI), as well. Initially, *ISBT 128* was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase the security and accuracy, and to permit unique unit identification globally. *ISBT 128* has now been extended to include cellular therapy products and tissues. ICCBBA is the not-for-profit organization ([www.iccbba.org](http://www.iccbba.org)) that is responsible for the development and maintenance of the *ISBT 128* standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support. Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) includes international representation from FACT, JACIE, ISCT, ISCT-Europe, ASBMT, EBMT, NMDP, WMDA, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of cellular therapy product codes, to draft labels and a labeling strategy for cellular therapy products, and to draft an implementation plan. The work of CTCLAG can be found in the following publications:

- Ashford, P. et al: *Standards for the Terminology and Labeling of Cellular Therapy Products*. *Transfusion* 2007; 47:1319-27
- Ashford, P. et al: *ISBT 128 Implementation Plan for Cellular Therapy Products*. *Transfusion* 2007; 47:1312-8

Product identification must use the product's proper name, attributes, and modifiers according to the standard terminology for cellular therapy products. This terminology can be found in the document titled, *ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions* at <http://iccbba.org/uploads/03/ea/03eade50519de4e5fd9c51a92dB10a05a/standardterminology.pdf>

The three main pieces of the standard terminology to unambiguously describe a product are class, modifiers, and attributes. Classes are broad descriptions of products (such as HPC, Cord Blood), modifiers describe the next step in categorization (such as Cryopreserved), and attributes are additional characteristics that uniquely define the product. A group of attributes, called Core Conditions, are required; these conditions include anticoagulant and/or additive, nominal collection volume, and storage temperature. There are also optional characteristics that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from donor and collection through the final processing. In some settings, such as where multiple additives are used, the additional information is part of the accompanying documentation, especially where label space is limited. It is not intended that products would be relabeled at the bedside, so attributes such as "thawed" would only be applied if that process occurred in the laboratory.

Cellular therapy products characterized in this standardized way can be designed using common, well-defined terms that are printed in eye-readable format on the label. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine-readable technologies such as bar codes. In this way, the products will be universally understood and international exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, the common major classes of products are defined as was current at the time of publication. No modifiers or attributes were included because of the sheer number and complexity and also, because this is a period of rapid growth in the use of *ISBT 128* for cellular therapy. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, ICCBBA is the appropriate authority for maintaining publications on current terminology. Facilities must use the terminology as defined in the ICCBBA document *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*, which is available at [www.iccbba.org](http://www.iccbba.org) > Subject Area > Cellular Therapy > Standard Terminology. CBBs should refer to Chapter Three, Cellular Therapy, for current terms and definitions related to cellular therapy. Inspectors will inspect the CBBs according to the current *ISBT 128* terminology and definitions.

If CB Processing Facilities have questions regarding *ISBT 128* terminology, they can reference the Standard Terminology document, view the ICCBBA website at [www.iccbba.org](http://www.iccbba.org), or contact ICCBBA directly for additional information and assistance. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product.

To utilize *ISBT 128* to its full advantage in the unique identification of products worldwide and in the use of common language, facilities should register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each CB unit's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their blood bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

**Evidence:**

Inspectors should examine the labels on site and the labeling process and procedures to verify the appropriate use of *ISBT 128* terminology is in use with the regard to class, modifiers and attributes. Inspectors should review Chapter Three, Cellular Therapy in the *ISBT 128* Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions (available at [www.iccbba.org](http://www.iccbba.org)) before conducting an inspection. It would be helpful to have the document available for reference during the inspection as well.

**STANDARD:**

*B6.1.2 If the CBB has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.*

**Explanation:**

The use of *ISBT 128* for all cellular therapy products provides a uniform coding and labeling system worldwide. *ISBT 128* is an international standard for the transfer of information associated with human tissue transplantation, cellular therapy, and blood transfusion. It provides for a globally unique donation numbering system, internationally standardized product definitions, and standard data structures for bar coding and electronic data interchange.

In the previous version of the Standards, *ISBT 128* terminology became mandatory. In a survey among cellular therapy facilities worldwide, it has been shown that although *ISBT 128* is being supported by FACT-accredited organizations, the transition towards full implementation of *ISBT*

128 is not yet completed by most of them. In this version of the Standards, an implementation plan of *ISBT 128* coding and labeling is mandatory. A paper to help centers implement *ISBT 128* is on the ICCBBA website (<http://www.iccbba.org/subject-area/cellular-therapy>).

**Evidence:**

The cellular therapy coding and labeling advisory group of ICCBBA has published the detailed terminology, and the use of these product codes needs to be verified. An *ISBT 128* implementation plan describing the steps necessary to implement *ISBT 128* within three years must be present.

**Example(s):**

The EU plans to implement a European Coding System in 2014. Inspectors of CBBs in the EU should take into account the uncertainty this pending system causes CBBs in terms of regulations in this area.

**STANDARD:**

*B6.2 Label Controls.*

*B6.2.1 Pre-printed labels.*

*B6.2.1.1 Labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the CBB Director or designee to confirm accuracy regarding identity, content, and conformity.*

**Explanation:**

New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects,
- Form or version number, if applicable,
- Legible and correct eye-readable information, and
- Identity to source (original) label that has been approved for use by the CBB Director or designee.

The CBB Director may designate the approval of labels to a suitable, qualified person but maintains ultimate responsibility.

**Example(s):**

The CBB Director may designate the approval of labels to someone from the CBB's quality unit.

**STANDARD:**

*B6.2.1.2 Stocks of unused labels representing different products shall be stored and maintained in a controlled manner to prevent errors.*

*B6.2.1.3 Unused obsolete labels shall be destroyed.*

**Explanation:**

Labels must be stored in a designated area where access is limited to authorized personnel. Stocks of unused labels for different products must be stored separately to prevent errors.

Only the current version of each label should be available for use in the processing area. Obsolete or unusable label stock should be defaced immediately to prevent their accidental use and then destroyed. However, as a controlled document, representative obsolete labels (or label templates) and their inclusive dates of service must be archived indefinitely.

**STANDARD:**

*B6.2.2 Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the CBB Director or designee.*

**Explanation:**

These requirements also apply to labels that are printed “on demand,” in which case the labels must be reviewed against an approved copy or template at each printing, and this review documented. It is recommended that the inspection of labels at receipt or after printing be performed by one person and independently verified by a second person. The process and outcome must be documented prior to release of the labels from the quarantine area.

The CBB Director may designate the approval of labels to a suitable, qualified person but maintains ultimate responsibility.

**Example(s):**

The CBB Director may designate the approval of labels to someone from the CBB’s quality unit.

**STANDARD:**

*B6.2.3 A system for label version control shall be employed.*

**Explanation:**

The document control system used for various parts of the label and what constitutes a label version must be defined by the facility or program. Any change in the label or label element that would change the interpretation of the label information would constitute a version change.

The CBB must have a documented process to account for all labels created for use in all stages of collection, processing, cryopreservation, and storage, including disposition of unused labels.

**Example(s):**

Labels may be organized physically or electronically so staff can readily identify the labels and be able to distinguish labels of different products from one another, e.g., by color-coding, size, or location. For example, labels used for related CB donations should be clearly segregated from those used for unrelated CB units.

A CBB could designate labels for each step in the process to minimize risks of mislabeling by beginning with 24 labels. Three (3) are used for original, in-process, and final unit, nine (9) are used for ancillary samples, six (6) are applied to paperwork, and three (3) are involved in reference lab submissions. Its process should indicate that the remaining three (3) are retained in the product file or discarded.

**STANDARD:**

*B6.2.4 Representative obsolete labels shall be archived indefinitely.*

**Explanation:**

Labels are controlled documents and need to be archived for reference. For on-demand labels, the template and an example demonstrating conformance with the template should be archived. Obsolete labels should be archived for as long as the current CB inventory has the labels.

**STANDARD:**

*B6.2.5 The label shall be validated as reliable for storage under the conditions in use.*

**Evidence:**

The results for validation studies of the labels under the conditions in use, including cryopreservation and storage, must be available to the inspector.

**STANDARD:**

*B6.3 Labeling Operations.*

*B6.3.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of CB units, associated samples, reference samples, maternal samples, and associated documents.*

**Explanation:**

Labeling operations must effectively allow the CBB to maintain the relationship between the CB unit and its samples and records. Applying the correct labels to units, samples, and documents is critical to accurately link test results, documentation, and donors.

The labeling SOPs should indicate that there are procedures in place for the items listed in the substandards to B6.2, including at a minimum:

- Receipt and quarantine,
- Verification of accuracy,
- Proper storage,
- Version control, and
- Destruction of obsolete labels.

CB units that were banked before FACT-NetCord accreditation or before this requirement was included in these Standards do not have to be relabeled to meet this particular requirement. However, all CB units banked at the time of accreditation or when this requirement was in effect must be in compliance.

**Evidence:**

Examples of all labels in use by the applicant CBB, including partial and in-process labels, will be provided to the inspector prior to the on-site inspection. Label content will have been pre-reviewed by the FACT office staff. On site, the inspector will verify that the labels submitted are in fact the labels in use at the facility. The inspector will focus more time on the labeling process, specifically assessment of its adequacy with respect to proper identification of CB units, associated samples, reference samples, maternal samples, and related documents. The inspector will observe the location where labels are stored to verify that the labels are organized in a manner to prevent errors.

**STANDARD:**

*B6.3.2 There shall be processes to verify that all labels in use are accurate, legible, and maintain physical integrity.*

**Explanation:**

Maintaining label accuracy must be addressed in the SOPs. While it is not required that the policy specifically mandates the number of labels used and the remaining labels be noted in each CB unit file, there must be adequate control of the process to minimize risk of mislabeling and mix-ups.

**STANDARD:**

*B6.3.2.1 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.*

*B6.3.2.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.*

**Explanation:**

This standard requires facilities to have a careful process for electronically transmitting information (such as with a bar code) and to double check the information rather than becoming solely dependent on the technology to work correctly.

**STANDARD:**

*B6.3.2.3 When the label has been affixed to the CB unit bag, a sufficient area of the bag shall remain uncovered to permit inspection of the contents.*

*B6.3.2.4 The information entered manually on the CB unit bag label shall be verified by at least two (2) staff members prior to allowing the CB unit to progress to the next stage of processing, storage, or distribution.*

**Evidence:**

The inspector will examine labeled CB units on-site to verify that labels are firmly attached or affixed and that sufficient area of the unit remains uncovered to allow examination of contents. Label elements that are required by governmental regulation must be clearly visible and any additional label requirements of Applicable Law must be present.

**STANDARD:**

*B6.3.2.5 All data fields on labels shall be completed.*

*B6.3.2.6 All labeling shall be clear, legible, and printed using ink that is indelible to all relevant agents.*

**Explanation:**

Ink used on labels must be indelible to relevant agents used in the process of CB banking. Indelible ink must also be used to record any information entered manually on the label. No fewer than two people must confirm that the manually entered information on the label is accurate. All data fields on a label must be complete; fields for which information is not required must be filled as not applicable or "NA." Labels must have been validated to confirm they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved CB units.

**Example(s):**

Relevant agents include liquids such as liquid nitrogen, alcohol wipes, and other liquids used around CB units.

**STANDARD:**

*B6.3.2.7 Labels affixed directly to a CB unit bag shall be applied using appropriate materials as defined by the applicable regulatory authority.*

*B6.3.3 CB units that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.*

*B6.3.3.1 The process to establish linkage between original and new labels shall be validated.*

*B6.3.3.2 This linkage shall be maintained as a permanent part of the CB unit record.*

**Evidence:**

If CB units are repackaged, the CBB needs to be prepared to show the inspector the labels on a repackaged unit to demonstrate that there are mechanisms in place (either on the label itself or via accompanying paperwork) to trace the unit from its origin to the final disposition.

**STANDARD:**

*B6.3.4 Integrally attached segments should be labeled with an identifier linking the segments to the applicable CB unit.*

*B6.4 Identification.*

*B6.4.1 There shall be a human-readable system and a machine-readable system in operation for identification for the CB unit, associated samples, reference samples, maternal samples, and associated documents.*

**Explanation:**

In addition to a machine-readable system, a human-readable component must also be included in case a scanner breaks and prevents machine-reading ability.

**STANDARD:**

*B6.4.2 Each CB unit shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any CB unit to its maternal and infant donor data, delivery information, family history, test results, and to all records describing the handling and final disposition of the CB unit.*

*B6.4.2.1 There shall be processes to ensure that the CB unit identifier is unique to prevent errors in identification.*

*B6.4.2.2 If a single CB collection is stored in more than one fraction, there shall be a system to identify each fraction.*

**Explanation:**

The unique identifier at the end of collection is not required to be the permanent barcode identifier that is assigned by the CBB. The combination of elements used to create a unique identifier may vary in different regions of the world where common names and/or birth designations may be inadequate. The elements chosen to create the unique identifier should be appropriate to the culture and region, and may not be the same from one bank to another. If the maternal name, medical record number, or dates of birth are used, they should not be observable by the courier or general public during transport to the facility where the permanent identifier is assigned.



It is permissible to assign the permanent unique identifier to the CB unit at the time of collection if it is done in a centralized and controlled process. However, barcode labeling may be more easily controlled when performed at the CB Processing Facility rather than at the CB Collection Site where maternal identifiers are much more familiar. The combination of mother's name, medical record number, and/or date of birth is unique in the environment of the CB Collection Site. This information is imperative to providing linkage with the subsequent identifier assigned by the CBB. There is actually more opportunity for error when pre-labeling tubes and bags for the CB Collection Site in hospital-based collections. A kit assembled for one delivery may be separated for use during another delivery, in which case multiple identifiers would be used for the collection of one CB unit and defer the potential to proceed with banking.

If a CBB uses multi-compartment bags for CB units, the identification system must be validated to confirm each fraction is identified during all stages of CB unit manufacturing.

**Example(s):**

The term "unique" refers to an identifier that is not used for anything else; for example, the following (each used alone) would not be considered to be a unique identifier for a CB unit: the medical record number used to identify a patient or mother of the infant donor, the medical record number used to identify the infant donor at the hospital, or a Social Security Number in the U.S.

Name, medical record number, and/or birth date may be used in a unique combination at the end of collection but must be linked to another identifier at least upon receipt into the CBB. For reasons of confidentiality (per FDA 21 CFR 1271.290(c) and 1271.55(a)(1)), once a donor eligibility determination has been made, U.S. CBBs may not use name, social security number, or medical record number as part of the unique identifier.

**STANDARD:**

*B6.4.3 Facilities may designate an additional or supplementary numeric or alphanumeric identifier to the CB unit, associated samples, reference samples, or maternal samples.*

*B6.4.3.1 Supplementary identifiers shall not obscure the original identifier.*

*B6.4.3.2 No more than one supplementary identifier shall be visible on a CB unit bag.*

*B6.4.3.3 The facility associated with each identifier shall be documented.*

*B6.5 The information provided on the label by the CB Collection Site shall be maintained indefinitely as part of the CB unit record.*

*B6.6 Label Content.*

*B6.6.1 There shall be processes to ensure the content of each label is compliant with Applicable Law and the requirements of these Standards.*

**Example(s):**

For U.S. CBBs that wish to submit a Biologics License Application (BLA), the U.S. FDA guidance, “Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications,” outlines specific regulations that apply to the label content for prescription drug products.

**STANDARD:**

*B6.6.2 Each label shall include at least the required information detailed in the Cord Blood Unit Labeling table in Appendix I and in the Modified Circular of Information Biohazard and Warning Labels table in Appendix II.*

**Explanation:**

The receiving facility address should be complete enough to ensure receipt of the CB unit at the CB Processing Facility.

The time zone is included in Appendix I for those CBBs that collect at CB Collection Sites outside the time zone of the CB Processing Facility. This information has bearing on the time in transit, time to processing, and time to cryopreservation.

Additives refer to any solutions added to the CB unit, including anticoagulants, sedimenting agents, and cryopreservation solutions. Even though the contribution of these additives may be minimal post processing, it is important that the transplant physician and recipient are aware of their presence to prevent or minimize a reaction to the infusion in the event that the recipient has a known allergy to an additive.

Date and time of distribution and the statements “Handle With Care” and “Medical Specimen” are required by European Directive. Since these are international standards and CB units can be distributed to Europe, assuring global compliance is reasonable.

A biohazard label must be attached or affixed to any CB unit from which a donor sample has tested positive for a relevant communicable disease (excluding CMV) or when donor screening indicates a risk factor for a relevant communicable disease or disease agents. Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products outlines when biohazard labels must be used. Biohazard labels can only be applied to units not required to be labeled biohazard when specific circumstances for their use are defined by policy. Biohazard labels must not be applied indiscriminately. These labels are meant to denote a greater hazard than that posed by any biological product. Using biohazard labels on all units without rationale that is documented in facility records is considered a deficiency unless such use is required by Applicable Law.

There have been concerns expressed that use of Biohazard labels on the product where it may be observed by non-medical personnel is in violation of Health Insurance Portability and Accountability Act (HIPAA) regulations in the U.S. as interpreted at some institutions. As a result, labels attached (via tie tag) may be preferred over affixed labels. In such cases, the tie tag can be positioned to minimize its exposure to the casual observer while providing the information needed for program personnel to take additional precautions when needed. The inspector should ask to see the SOP that defines the conditions for using a Biohazard label and

determine if the facility's procedures are adequate and appropriately safe to prevent transmission of infectious disease.

Warning labels with or without a Biohazard label are required when CB unit testing or screening is positive for infectious disease risk or is incomplete. The exact statements that are required differ for autologous and allogeneic products. The table in Appendix II details the circumstances under which these warnings are required. The Standards require that autologous and allogeneic products be tested for communicable disease.

The labeling applies to the restrictions in effect at the time of collection. Although there may be a risk associated with prolonged incubation period of virus in countries added to the list post collection, that risk is considered minimal.

When a CB unit is shipped (such as by truck or airplane without trained personnel), statements such as "Do Not X-Ray," "Medical Specimen," "Handle with Care," and shipper handling instructions must be affixed to the outer container. This includes CB units shipped from a remote CB Collection Site to a CB Processing Facility or from the CBB to a Clinical Program.

**Evidence:**

The inspector will confirm that Biohazard labels and warning statements are utilized as described in Appendix II. Autologous product labels must have the statement "Not Evaluated for Infectious Substances" present when the donor screening does not contain all of the elements required by these Standards.

The CBB must show the inspector CB unit labels for units distributed under an IND and under a BLA, as applicable, to demonstrate the appropriate statements are used on the unit or in the accompanying record (the infusion form or distribution record) issued with the unit. The inspector will verify that they are distributed with the required statement on the label or in the accompanying records.

**Example(s):**

There are a number of mechanisms to comply with the requirement to label CB units as biohazardous:

- When an infectious risk is determined by testing that was not completed at the time of cryopreservation, a CBB may choose to attach a Biohazard label to the unit and maintain it in quarantine storage. However, for units frozen with overwrap, attaching a tie tag can be impossible, and that information should accompany the unit.
- When infectious disease testing is positive and the CB unit is retained, some CBBs may elect to place the Biohazard label in the accompanying records.

Per FDA donor screening requirements, CB units are ineligible if communicable disease testing was performed in a non-CLIA certified lab or if the donor is a resident of a country in the USDA BSE list. A list of countries at risk can be found at

[http://www.factwebsite.org/Standards\\_and\\_Resources/Subpages/Donor\\_Questionnaire.aspx](http://www.factwebsite.org/Standards_and_Resources/Subpages/Donor_Questionnaire.aspx).

CB units that are regulated under the U.S. FDA 351 regulations must be either distributed under a BLA or an IND. If distributed under an IND, the unit must be labeled with the statement "Caution: New drug limited by federal law for investigation use only." Such CB units must contain this statement attached or affixed to the label or accompanying the unit.

The label or accompanying records for licensed CB units must include the statement “Rx Only” indicating that the unit may only be distributed by a prescription from the transplant physician. The physician order form required by these Standards may serve as the prescription.

Labeling requirements for the UK can be found in the *Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment*. This guide is available at:

[http://www.hta.gov.uk/db/documents/Annex\\_-\\_Guide\\_to\\_Quality\\_and\\_Safety\\_Assurance\\_for\\_Tissues\\_and\\_Cells\\_for\\_Patient\\_Treatment.pdf](http://www.hta.gov.uk/db/documents/Annex_-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf).

**STANDARD:**

- B6.6.3 A CB unit bag with a partial label shall be accompanied by the required information detailed in the Cord Blood Unit Labeling table in Appendix I attached securely to the CB unit on a tie tag or enclosed in a sealed package to accompany the CB unit.*
- B6.6.4 A partial label at a minimum shall be present on the CB unit during all stages of processing.*

**Explanation:**

A minimum of a partial label is required on the CB unit. Additional information may be attached to the unit via a tie tag or be present on accompanying paperwork as long as the paperwork is included in the secondary bag (such as a zip lock bag) with the unit. It is not acceptable to transport multiple units from different donors using partial labels in a single secondary bag or with all of the additional information on a single inventory sheet. Labels applied during processing may be partial labels (in-process labels). This is the only case where partial labels are acceptable without additional information in an enclosed secondary container. Appropriate modifiers should be applied to the label while the CB unit is undergoing different stages of processing to allow other qualified lab personnel to identify which steps in the process have been completed.

These Standards require that partial labeling information be present on the CB unit during all stages of processing. Only the CB unit needs a partial label; other portions do not have to have a partial label but must have at least some identifier.

In CBBs where both related and unrelated banking occurs, CB units collected for related use must be labeled in a manner that obviously and immediately separates them from the unrelated allogeneic inventory to ensure that a related unit is not available for unrelated use.

**Evidence:**

If the CBB uses a partial label at any stage in collection, distribution, processing, cryopreservation, or storage, the CBB must show the inspector the labeling SOP describing the use of that partial label, an example of the partial label, and the process for providing the additional information that is not included on the partial label.

**Example(s):**

Though the CB unit may transiently occupy a syringe during a transfer from one container to another, the syringe itself would not be considered the actual CB unit. So long as it is a mechanism used to transfer the CB unit, bearing just the unique identifier is sufficient.

**STANDARD:**

*B6.7 Elements detailed in the Accompanying Documents at Distribution to a Clinical Program table in Appendix III shall accompany the CB unit at distribution to a Clinical Program according to Applicable Law.*

**Explanation:**

The records referred to in this standard are source documents and the information used to perform the donor eligibility determination.

These Standards allow for CB units obtained from ineligible donors to be distributed for infusion provided that there is documented medical need that the unit be used despite the potential risks to the recipient. Use of CB units from an ineligible donor requires documented approval of the CBB Medical Director that includes the reason that the donor was ineligible, and documentation that the physician administering the CB unit has been notified of all testing and screening results.

CB units that are needed for infusion before all required donor screening and testing are complete may also be distributed provided that the distribution documents (for example, the product infusion form) include a statement that eligibility determination is not complete, the results of the testing that has been completed, a list of required testing or screening that has not been completed, and documentation that the transplant physician was notified of the incomplete testing or screening. It should be the CBB Medical Director in concert with the attending physician, rather than the CB Processing Facility personnel, who determine if a request for CB unit release prior to completion of testing is warranted. Such a situation would likely fall under the category of a non-conforming unit and would require exceptional release and CBB Medical Director agreement.

At the time of distribution, the CB unit must be accompanied by a document that contains instructions for administration that include methods to prevent the introduction, transmission, or spread of communicable disease. A “Circular of Information for the Use of Cellular Therapy Products” document (prepared jointly by the AABB, American Association of Tissue Banks, American Red Cross, American Society for Blood and Marrow Transplantation, American Society for Apheresis, America’s Blood Centers, Foundation for the Accreditation of Cellular Therapy, ICCBBA, International Society for Cellular Therapy, and National Marrow Donor Program) contains information that is suitable for this purpose. This document can be found on the FACT website at [www.factwebsite.org](http://www.factwebsite.org).

The CB Processing Facility must inform the transplant physician of the results of any testing or screening that was completed after the product was distributed. The provision of this information must be documented in the processing records. If any result is positive, it is the responsibility of the physician to notify the recipient and to document patient notification in the clinical record.

**STANDARD:**

*B7 EQUIPMENT*

*B7.1 All critical equipment shall be defined, qualified, and validated for the intended use.*

*B7.1.1 Equipment shall be used in accordance with the manufacturer's instructions.*

**Explanation:**

Qualification of equipment establishes confidence that equipment functions consistently within established limits. However, the manner in which equipment is used must also be validated.

**Example(s):**

A change in equipment to a new controlled rate freezer might require qualification of the freezing program to confirm that the freezing parameters meet the predetermined specifications. A validation study may be performed by freezing CB units under the parameters to be used to preserve viability of the CB units.

**STANDARD:**

*B7.2 Equipment shall be used in a manner that prevents CB unit mix-ups, contamination, and cross-contamination, and that does not compromise unit function and integrity.*

*B7.3 Equipment shall conform to Applicable Law.*

**Explanation:**

While it cannot be guaranteed that the viability will not be affected or that adventitious agents will not be introduced, a CBB can take reasonable precautions to prevent or limit the occurrence. Every effort must be made to ensure that equipment used does not alter the viability of the CB unit, allow for introduction of adventitious agents, or transmit or spread communicable disease. Initial qualification of equipment, validation for its intended use, and periodic audits will help confirm that the equipment is performing as required. If there is an occurrence of introduction of adventitious agents or the transmission or spread of communicable disease, the CBB should investigate, report, and prevent future occurrences through its corrective action policies.

**STANDARD:**

*B7.4 Equipment records shall include the manufacturer's name, serial number or other identifier, manufacturer's instructions, equipment location, and use of each piece of equipment, including the identification of each CB unit for which the equipment was used.*

*B7.4.1 Equipment records shall be maintained for a minimum of 10 years after distribution of the CB unit.*

**Example(s):**

If the CBB can demonstrate traceability of the equipment identification within the CB unit records, documenting for which CB unit the equipment was used within the unit records is acceptable. However, the CBB should consider how it will identify which units were affected by an issue with equipment in a manner that will allow for expediency and accuracy.

**STANDARD:**

*B7.5 Calibration.*

- B7.5.1 Equipment shall be observed, tested, and calibrated on a regularly scheduled basis as recommended by the manufacturer, after a critical repair or move, and, at a minimum, annually.*
- B7.5.2 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.*
- B7.5.3 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for CB units manufactured during the period of uncertainty.*
- B7.5.4 Records of the dates and copies of calibration results shall be maintained.*

**Explanation:**

Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the CBB. Maintenance and calibration are required to detect malfunctions and defects and to confirm that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control.

Tags or stickers should be visible on the equipment indicating that quality control (QC) parameters have been met, the date QC testing was performed, and when such testing is next due. Where applicable, calibration procedures should include limits for accuracy and precision.

Equipment identified by the CBB to have a critical measuring function, such as thermometers, timers, and scales, must be calibrated against a traceable standard. A traceable standard is one that can be directly linked to a provider that has documented the accuracy of the measuring device.

When equipment is found to be out of calibration or specification, the validity of previous measurements and decisions based on those measurements should be reviewed. There should be documentation that the CB units manufactured during this period of uncertainty have been evaluated and determined to be conforming to specification or corrective action has been documented. This should include an investigation of potential adverse events to manufactured products using the equipment tracking system. Note that if critical equipment used in processing is located outside of the CBB, such as sterilization equipment, it is the CBB's responsibility to confirm that equipment is properly maintained and calibrated.

**Evidence:**

Calibration records can be used to confirm that traceable standards have been used. SOP(s) describing the corrective action to be taken when precision and accuracy limits are not met and written instructions to be followed if the equipment fails must exist. Records to document these activities, including investigation of potential adverse events caused by cellular therapy products, should be present.

Schedules may vary among CBBs, based on frequency of use, performance stability, or recommendations from the manufacturer. Recent records of regularly scheduled maintenance and QC should be readily available for each piece of equipment.

**Example(s):**

Examples of traceable standards include National Institute of Standards and Technology (NIST) reference thermometers, stop watches, and tachometers. Other vendors may provide similar products but they must have a direct link to records indicating accuracy to a known standard. An alternative to using the actual traceable standard is to calibrate a similar device against the traceable standard and use the newly qualified device for routine measurements. If a traceable standard cannot be obtained, then the CBB must document how the accuracy of the measurement reading was determined.

**STANDARD:**

*B7.6 Maintenance and repairs.*

*B7.6.1 Equipment shall be maintained in a clean and orderly manner and located so as to facilitate cleaning, disinfection, calibration, and maintenance according to established schedules.*

*B7.6.2 Records of the maintenance schedule; maintenance performed; and damage, malfunction, modification, or repair to equipment shall be maintained.*

*B7.6.3 There shall be a procedure that addresses the actions to take in the event of equipment malfunction or failure.*

**Explanation:**

In addition to the regular maintenance schedule and maintenance after repairs, the CBB also needs to perform the necessary maintenance and repairs after moving equipment.

**STANDARD:**

*B7.7 Cleaning and sanitation.*

*B7.7.1 Equipment shall be cleaned and sanitized according to established schedules.*

*B7.7.2 Records of equipment cleaning and sanitation shall be maintained.*



*B7.8 Equipment shall be routinely inspected for cleanliness, sanitation, and calibration and to ensure adherence to applicable equipment maintenance schedules.*

*B7.8.1 Equipment shall be routinely inspected for compliance to cleaning and maintenance schedules.*

*B7.9 Records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be displayed on or near each piece of equipment.*

**B8 SUPPLIES AND REAGENTS**

*B8.1 Vendors for all critical reagents and supplies shall be qualified.*

**Explanation:**

Criteria for selecting vendors for critical reagents and supplies must be written and reasons for their selection must be justified.

**Example(s):**

Surveys of critical vendors may be conducted to provide a description of their quality plan and operations, and to determine if the vendor can provide the necessary supplies and reagents and comply with the appropriate Standards. Depending on risk, on-site audits may be performed.

**STANDARD:**

*B8.2 Critical reagents and supplies shall be defined and qualified to function as expected.*

*B8.3 Supplies and reagents shall not adversely affect the viability of the CB unit and shall not permit the introduction of adventitious agents or the transmission or spread of communicable disease.*

*B8.4 Supplies and reagents that come into contact with the CB unit shall be sterile.*

*B8.4.1 Sterilization of supplies and reagents prepared within the facility shall be documented.*

*B8.5 Supplies and reagents should be used in a manner consistent with instructions provided by the manufacturer.*

*B8.6 Supplies and reagents used for CB collection, processing, or cryopreservation, whenever possible, shall be approved for human use.*

*B8.6.1 Supplies and reagents shall be of the appropriate grade for the intended use.*

*B8.7 Certificates of analysis shall be obtained and maintained indefinitely on file for all critical reagents.*

*B8.8 Receipt, inspection, verification, acceptance, and storage of supplies and reagents shall be documented.*

*B8.8.1 The disposition of rejected supplies and reagents shall be documented.*

*B8.9 The lot number, expiration date, and manufacturer of supplies and reagents used for the collection and processing of each CB unit shall be documented.*

**Explanation:**

Whenever possible, supplies and reagents that come into contact with cord blood (CB) units must be approved for human use. If there are no suitable supplies or reagents approved for human use, those used must be clinical or pharmaceutical grade, as appropriate, and free of microbial contamination. For simple, routine collection, processing, or cryopreservation of CB units, several reagents that are of clinical or pharmaceutical grade have been identified, and results of the studies utilizing these reagents have been published in the peer-reviewed medical literature for over 20 years.

Where there are no suitable clinical or pharmaceutical grade reagents available for the processing that is being conducted or for reagents being used under approved research purposes, the reagents meeting these criteria shall be qualified. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency,
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute, or
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

If a reagent is not of the appropriate grade, it should be of the highest grade (or purity) available and the CBB must validate that the reagent is safe and effective for the specified purpose. Any reagents generated in-house for use in CB unit processing must be qualified and validated for their intended use.

For example, each new lot of cryopreservation medium, such as DMSO, must be verified beyond the initial qualification to perform as expected and is sterile.

Reagents and supplies that are received into the facility shall be examined for contamination, breakage, discoloration, etc. before they are placed into the facility's inventory and made available for use. There shall be an SOP describing this process and the results of the examination should be documented. Records must be kept of the receipt of each supply or reagent including the type, manufacturer, lot number, dates of receipt, and expiration date. There must be a mechanism to link the supplies and reagents, lot numbers, and expiration dates to each CB unit manufactured.

The inventory control system must be adequate to prevent the use of outdated or damaged supplies and reagents. There should be a mechanism to monitor the flow of supplies and reagents within the facility to prevent the use of outdated supplies and reagents. This mechanism can be tracked on paper or via a computer program.

**Evidence:**

Records of reagent qualification and, if indicated, validation of its intended use must be available. Qualification may be performed by the CB Collection Site, the CB Processing Facility, or the manufacturer. In the case of manufacturer qualification, the certificate of analysis should be available in the facility. Records pertaining to supplies and reagents shall be maintained.

**Example(s):**

The definition and requirements for each critical reagent and supply may be listed on a specification sheet. Information on this sheet may include a description of the product, the catalog number, transportation requirements, required documentation (e.g., certificate of analysis), qualification checks to be performed, acceptance criteria, and storage conditions.

Verification of each new lot of cryopreservation medium may be performed by comparing post-thaw CFU or viable CD34 recovery with the current batch of cryopreservation medium.

U.S. CBBs should refer to FDA 21 CFR §1271.210 regarding supplies and reagents.

**STANDARD:****B9 INVENTORY MANAGEMENT**

*B9.1 The inventory management system shall clearly distinguish related CB units from unrelated CB units.*

*B9.2 The inventory management system for CB units shall allow each CB unit and its associated samples, reference samples, maternal samples, and records to be located in a timely way. The inventory records shall include:*

*B9.2.1 CB unit unique identifier.*

*B9.2.2 Maternal donor identifier.*

*B9.2.3 Storage device identifier.*

*B9.2.4 Location within the storage device.*

**Explanation:**

Mechanisms must be in place to facilitate the retrieval of CB units and samples at any time when needed. Processes in a CBB are complicated by the fact that multiple samples of varying types and storage requirements are maintained. Furthermore, CB units may be in transitional quarantine until placed in permanent storage, which may dictate separate locations and necessitate transfers. Therefore, the inventory management plan must include a system of documentation and audits to confirm the system is functioning properly.

**STANDARD:**

*B9.3 The inventory management system shall be designed to prevent mix-ups, contamination of the CB units during storage, and the improper release of CB units.*

**Explanation:**

Improper release refers to the transfer of CB units to general storage before the CB unit has been approved to have met all applicable release criteria.

**Example(s):**

U.S. CBBs should refer to FDA 21 CFR 1271.260 regarding storage.

**STANDARD:**

*B9.4 The inventory management system shall be designed to address the duration of storage for cryopreserved CB units, including assigning an expiration date to CB units where appropriate.*

**Explanation:**

The definitive expiration date for CB units is currently unknown due to different processing and storage methods and the effects of long-term storage on CB unit potency. Therefore, expiration dates are not dictated by the Standards. Rather, these should be determined based on the CBB's own viability and recovery data. If no expiration date has been established, this should be documented. CBBs are required to establish policies for the duration and conditions, including validation of storage, and are encouraged to generate data to use for decision making in the future.

**STANDARD:**

*B9.5 The CBB shall have policies related to the return of CB units to the CBB inventory.*

*B9.5.1 Unrelated allogeneic CB units shall not be returned to the CBB inventory after they have left the CBB premises.*

*B9.5.2 If related CB units are returned to the CBB inventory, there shall be documentation of appropriate storage and transportation.*

**Explanation:**

Return of unrelated CB units is not permitted in part as a protection for the CBB. CBBs must verify that the Clinical Programs are prepared to accept responsibility for the shipment prior to its release from the CBB. If a related unit is returned, the CBB must document that storage and transportation throughout the time the unit was away from the bank was within the specified parameters.

**STANDARD:**

*B10 INVENTORY TRANSFER*

*B10.1 If all or part of a CB unit inventory is to be transferred to another CBB:*

*B10.1.1 The CBB shall have policies and Standard Operating Procedures describing the transfer of inventory.*

*B10.1.2 There shall be a written agreement between the transferring and accepting CBBs that describes the responsibilities of each CBB, including the elements in B10, at a minimum.*

**Explanation:**

The written agreement between the transferring and accepting CBBs must describe which bank has responsibility for the elements listed in this section of the Standards. Early communication between the two banks is necessary so that all information required for future storage of the inventory is available. This communication needs to happen before the agreement is signed so that the banks are certain that the receiving bank has the records, storage space, and other requirements needed to protect the CB unit inventory.

**Example(s):**

One of the requirements in this section is that the transferring CBB informs the receiving bank the manufacturer and dimensions of the CB unit bag and canister. It is critical that this information is shared in advance in case the receiving bank does not have the freezers necessary to accommodate the units.

**STANDARD:**

*B10.1.3 There should be a mechanism to contact the transferring CBB Director or designee for future reference, as defined in the contract or agreement.*

**Explanation:**

There should be a mechanism by which the CBB Director or designee of the transferring CBB can be contacted for information regarding CB units transferred from the CBB. This period of time must be defined in the contract or agreement.

**STANDARD:**

*B10.2 Inventory transferred to another CBB shall be accompanied by the following at a minimum:*

*B10.2.1 All collection and processing records, including at a minimum:*

*B10.2.1.1 Medical and genetic history.*

*B10.2.1.2 Identity and results of all maternal and CB unit testing.*

*B10.2.1.3 A summary of records used to make the donor eligibility determination.*

*B10.2.1.4 Cryopreservation records, including freezing curve.*

*B10.2.2 All associated samples, reference samples, and maternal samples.*

*B10.2.3 The complete storage history of the CB unit inventory in a way that the history of individual CB units can be traced, including the storage temperature records and records of any transfer of the inventory to a different storage location.*

**Explanation:**

While storage history does not need to be provided for individual CB units, the information must be provided in a way that a CBB can trace the history of individual units in question.

**Evidence:**

If conditions are modified during any time in the CB unit's history, it should be reflected in the CB unit record.

**Example(s):**

A transferring bank may provide a CBB with batch records that show when a group of CB units was moved to a new freezer. If cell viability of a CB unit needs to be investigated, the CBB must be able to use those batch records to determine if the CB unit was in that relocated group.

**STANDARD:**

*B10.3 The transferring and accepting CBBs shall collaborate to ensure that:*

*B10.3.1 The inventory is transferred in a manner that maintains proper storage temperature and prevents mix-ups and contamination.*

*B10.3.2 Transport and shipping does not adversely affect the integrity of the CB units.*

*B10.3.3 The safety of transporting and shipping personnel is ensured.*

*B10.3.4 The accepting CBB is notified of the manufacturer and dimensions of the storage bag and canister to properly store the CB unit.*

**Explanation:**

It is vital that a Clinical Program and its Processing Facility are informed about the CB unit being shipped so preparations can be made for transfer of the unit to proper storage upon arrival. Relaying the number of canisters and their physical dimensions allows the receiving facility to determine a location for storing the CB unit. A receiving Clinical Program insufficiently equipped to properly accommodate CB units could compromise the integrity of the CB units while identifying an appropriate storage location.

**STANDARD:**

*B10.4 There shall be policies to maintain confidentiality.*

*B10.5 Responsibilities of the accepting CBB.*

*B10.5.1 Records shall be in a language and form that can be understood by the accepting CBB personnel.*

**Explanation:**

If the records are not in the language of the receiving CBB, they should be translated using a certified translation service.

**STANDARD:**

*B10.5.2 There shall be documentation of review of records and of transferred inventory to verify that the CB units meet the requirements of the written agreement for transfer of inventory.*

*B10.5.3 Transferred records shall include at a minimum:*

*B10.5.3.1 Maternal consent.*

*B10.5.3.2 Medical and genetic history.*

**Evidence:**

The completed medical questionnaire should be included with the medical and genetic history.

**STANDARD:**

*B10.5.3.3 Identity and results of all maternal communicable disease tests, and, if performed, the identity and results of all CB unit communicable disease tests.*

*B10.5.3.4 All results from testing performed on the CB unit, including CB unit cell counts and sterility testing.*

*B10.5.3.5 Processing information.*

**Example(s):**

Processing information may include information regarding confirmation that key steps were verified to meet expected endpoints, raw cell counts, confirmation that critical materials were used prior to expiration, etc.

**STANDARD:**

*B10.5.3.6 Cryopreservation records, including freezing curve.*

*B10.5.3.7 The manufacturer and approximate dimensions of the storage bag and canister.*

*B10.5.3.8 Number of attached segments and other reference samples.*

*B10.5.3.9 Other records as required to allow the receiving CBB to meet these Standards.*

*B10.5.4 There shall be a process for inspecting incoming CB units for damage and contamination.*

*B10.5.5 After the CB units have been transferred, but before the transferred inventory is made available for search:*

*B10.5.5.1 The integrity and viability of thawed CB units shall be verified to confirm the transport or shipping method did not compromise CB unit viability.*

**Explanation:**

The CBB must verify the transport or shipping method did not compromise CB unit viability. To do this, the CBB can set up a study using a sampling of CB units that were all handled in the same manner.

**STANDARD:**

*B10.5.5.2 There shall be confirmation of the completeness of all records as described in B10.5.3.*

*B10.5.5.3 The accepting CBB shall determine whether to accept, reject, or place in quarantine incoming CB units based on established criteria designed to prevent the transmission of communicable diseases.*

**B11 DOCUMENTS AND RECORDS REQUIREMENTS**

*B11.1 A record management system shall be established and maintained to allow for protection, preservation, integrity, and ready retrieval of records.*

*B11.1.1 Records shall be available for inspection by authorized individuals upon request from a regulatory or accrediting agency.*

*B11.2 If records are maintained in more than one location and/or format, there shall be a system for prompt identification, location, and retrieval of all records.*

**Explanation:**

Each CBB has the flexibility to develop individualized systems of maintaining and organizing records as long as certain objectives are achieved. Records may be maintained in more than one location, provided that the records management system is designed to allow prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in an SOP.

Electronic records must be backed up on a regular basis and stored to prevent their loss. In the event that the CBB ceases operation, it must make provisions for all records to be maintained for the required period.

Records include quality control, personnel training and competency, facility maintenance, facility management, and other general facility records.



Facility maintenance records include documentation of dates and extent of repairs on mechanical systems, dates and extent of renovations and new construction; preventative maintenance on equipment; personnel responsible for cleaning; additional training records when required; safety training for biological, chemical, and radiation exposure and/or disposal; and the outcome of any building and/or facility inspections for safety and/or compliance with governmental and/or other agencies.

Facility management records include management issues related to facility maintenance including a list of responsible individuals with job titles and areas of oversight and resolution of facility problems.

**Evidence:**

It is suggested that CBBs have a minimum of the previous three years' records readily accessible to the inspector for review.

**Example(s):**

It is recommended that recent records should be kept on-site and archived records should be readily accessible within a reasonable time frame. Records may be maintained electronically, as original paper records, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm.

**STANDARD:**

*B11.3 Identity and medical records of the infant donor and family shall be in a language understood by the CBB personnel, registry, and/or Clinical Program.*

*B11.3.1 Records of CB units manufactured in or exported to the U.S. shall be in English or, if in another language, shall be translated to English and accompanied by a statement of authenticity by the translator prior to release of the CB unit.*

*B11.4 The following CBB records shall be maintained indefinitely:*

**Explanation:**

Indefinite does not necessarily mean permanent. Indefinitely is defined as a timeframe without a fixed or specified limit. CB banking is a young field in which CB units could conceivably be stored indefinitely. The standard requiring indefinite storage of associated records that describe the manufacture of a CB unit is intentionally conservative.

The records in B11.4 must be maintained indefinitely but not all need to be immediately available. They may be in long-term storage facilities. CBBs should refer to Applicable Law for specific requirements related to their location and activities.

**Example(s):**

U.S. CBBs should refer to FDA 21 CFR 1271.270(b) setting forth requirements for records management systems.

**STANDARD:**

*B11.4.1 Infant donor and parental records.*

**Explanation:**

These include all records in Section C of these Standards. Donor/recipient files (either electronic or hard copy) must be maintained with a secure system that is designed to guarantee absolute confidentiality and is in compliance with U.S. HIPAA regulations, or applicable equivalent confidentiality and privacy regulations. The inspector should be alert to breaches in policy that potentially compromise donor/recipient confidentiality.

This standard relates to records relevant to performing donor eligibility determination.

**Evidence:**

Inspectors should review the documentation at the CBB and not request documentation from the Clinical Programs.

**STANDARD:**

*B11.4.2 CB unit records related to collection, processing, storage, and distribution.*

**Explanation:**

The CB unit record includes all records related directly to the collection, processing, testing, banking, selection, and/or release of CB units, including research protocols. It shall be maintained and organized in such a way as to facilitate review of the CB unit history before making it available for distribution and, if necessary, subsequent to the CB unit's release as part of a follow-up evaluation or investigation. If records are maintained in more than one location, the records management system shall be designed to allow prompt identification, location, and retrieval of all records.

The supplies and reagents used on the CB unit during collection and processing need to be recorded. If the supplies and reagents are provided by the CBB in a kit, the kit should be identified. If the supplies and reagents are provided to contracted facilities in bulk, there should be a mechanism to identify the source of the individual supplies and reagents to allow recording of or tracing to the manufacturer or supplier, lot number, expiration date, date of receipt, and relevant verification.

In CBBs where kits are supplied to the CB Collection Site, it is the responsibility of the CBB to maintain records for reagents and supplies provided. If the CBB provides CB Collection Sites and/or contracted CB Processing Facilities supplies and reagents for CB collection and/or processing, it must have on record the information for those materials that it distributed to the sites.

All records are not required to be in every location where CBB activities occur. However, the CBB facility must have a mechanism to control and access all records, regardless of where the activity occurs.

**STANDARD:**

*B11.4.3 QM records.*

**Explanation:**

QM records include the results of audits, errors, accidents and adverse reactions reports, and outcome analysis.

**STANDARD:**

*B11.4.4 Personnel records.*

**Explanation:**

Personnel training and competency records include qualifications, licenses and/or certifications, initial training documents, and competencies for cognitive and procedural skills.

**Evidence:**

The CBB is only responsible for storing employee records. Collection personnel that perform a scope of activities related to the collection of CB for banking but are not employees of the CBB must be identified. To maintain confidentiality, the inspector only needs to see records that pertain to requirements in these Standards.

**Example(s):**

Records of collection staff training and competency may be located either at the CB Collection Site or at the CBB. Either is acceptable so long as the records are available for review and meet this standard. If the collection staff records are not stored at the CBB, there must be an agreement to transfer these records to the CBB if the retention policies differ.

**STANDARD:**

*B11.5 Facility cleaning and sanitation records shall be retained for three (3) years at a minimum.*

**Explanation:**

The minimum retention period of three years is based upon the U.S. FDA's GTP requirements.

**STANDARD:**

*B11.6 Equipment maintenance, inspection, calibration, and sterilization records shall be retained indefinitely.*

*B11.7 Records in case of divided responsibility.*

*B11.7.1 If two (2) or more facilities participate in donor management or the collection, processing, testing, cryopreservation, storage, listing, search, selection, reservation, release, or distribution of the CB unit, the records of each facility shall plainly show the extent of its responsibility.*

*B11.7.2 The CBB shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a CB unit.*

*B11.7.3 There shall be a system to allow the CBB access to information that tracks all manufacturing steps performed by other facilities.*

*B11.7.4 Each participating facility shall furnish to the facility of final disposition a copy of CB collection and processing records related to the safety of the CB unit.*

**Explanation:**

Records may be as general as naming the facility that collected the CB or as specific as the staff member performing phlebotomy for IDM specimens, physical assessment for risk factors, and performing the actual CB collection. This is described in the CBB's policies and can be evidenced through a tracing approach to inspection.

**STANDARD:**

*B11.8 Electronic Records Requirements.*

*B11.8.1 The CBB shall establish and maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the CBB that are used:*

*B11.8.1.1 In lieu of paper.*

*B11.8.1.2 To make decisions.*

*B11.8.1.3 To perform calculations.*

*B11.8.1.4 To create and/or store information used in critical procedures.*

**Explanation:**

The definition of an electronic record is, "A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer." This Standard requires CBBs to establish and maintain a current listing of all critical electronic record systems specific to CB banking. As CBBs utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic records are considered critical when they are:

- used in lieu of paper,
- used to make decisions based upon the data stored and/or created by the electronic record system (including outcome analysis),
- used to make calculations via automated functions, and/or
- used to create and/or store pieces of information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting

organizations. Furthermore, CBBs may not have the authority to direct validation studies on these systems.

**Evidence:**

The CBB's list of critical electronic record systems must include all electronic record systems used by the CBB that meet the criteria in this standard.

**Example(s):**

Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

**STANDARD:**

*B11.8.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to ensure the accuracy, integrity, identity, and confidentiality of all records.*

*B11.8.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.*

*B11.8.2.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.*

*B11.8.2.3 All critical electronic record systems shall ensure that all donor and CB unit identifiers are unique.*

*B11.8.3 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation of the CBB in the event that critical electronic record systems are not available. The alternative system shall be validated and CBB staff shall be trained in its use.*

*B11.8.4 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.*

*B11.8.4.1 A method shall be established or the system shall provide for review of data before final acceptance.*

*B11.8.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.*

**Explanation:**

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and back-up processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as procedures are revised and issues with the use of critical electronic record systems are identified.

The final review and acceptance of entered data does not require a second individual to verify the data, nor does the identification of individuals responsible for record entries need to be automated. The intent of the standard is to require all data to be verified as correct and to require maintenance of documentation of who has entered pieces of information.

Unambiguous identification is necessary not only for record creation, but also changes to existing records. Such identification provides an audit trail useful for investigation into adverse events and deviations.

**Example(s):**

To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's login credentials.

**STANDARD:**

*B11.8.5 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.*

*B11.8.6 For all critical electronic record systems, there shall be validated procedures for and documentation of:*

**Example(s):**

The FDA guidance titled, *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (2002) provides recommendations for validating electronic record systems. This guidance is available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf>

Some CBBs have Information Technology (IT) departments that manage the electronic record system. The inspector can confirm compliance with many of these standards by talking to representatives from that department if necessary.

**STANDARD:**

*B11.8.6.1 Systems development.*

*B11.8.6.2 Numerical designation of system versions, if applicable.*

*B11.8.6.3 Prospective validation of system, including hardware, software, and databases.*

*B11.8.6.4 Installation of the system.*

*B11.8.6.5 Training and continued competency of personnel in systems use.*

**Explanation:**

It is critical that the current version of the policies and SOPs be available to the CBB personnel at all times. Electronic versions are acceptable, but the CBB must have plans for management of computer system down time and document control and a method to access them must be available at all times, even in power failure.

**Evidence:**

Whether available electronically or in conventional paper format, inspectors should verify that the SOP available at the time of inspection is the one currently in use.

**STANDARD:**

*B11.8.6.6 Monitoring of data integrity.*

*B11.8.6.7 Back-up of the electronic records system on a regular schedule.*

*B11.8.6.8 System maintenance and operations.*

*B11.8.7 All system modifications shall be authorized, documented, and validated prior to implementation.*

**Explanation:**

This standard is not meant to require CBBs to assume responsibility for hospital-wide data systems. Any data system that does exist within the scope of control of the CBB is required to meet these Standards.

Establishment of an electronic record keeping system that meets one or more of the criteria for a critical electronic record system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor or consultant, or developed from off-the-shelf software.

Each CBB must determine in advance whether the staff will depend on an electronic record or a paper record system to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

Validation procedures of critical electronic systems include, as appropriate, such things as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under “worst case” scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed such as too many programs open on a Windows desktop), power failures, etc.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information with limited choices for data consistency.
- Source data is derived from pre-defined sources such as fixed forms. “Monitoring for data integrity” means establishing assurances that data has not been changed either by accident or by intent, and requires access to original documents whenever possible

along with a plan for verification of the electronic system data by comparison to original data.

- Evidence of a schedule of regular back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails.
- A mechanism to report deviations so that problems are reported and resolved.
- Evidence that changes to records do not obscure previously entered information.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

As with all other cellular therapy processing activities, the staff members who utilize the electronic record system must be trained for such use. Moreover, just as SOPs are required for cell manipulations, SOPs must also be in place to describe how to enter, process, and retrieve data using the electronic record system. Competency of staff using the system must be documented on a regular basis (annually at a minimum), and must also be documented with changing versions of the systems in use.

In case of error or ambiguity, a method must exist to allow traceability of data entered into the electronic record system to the staff member who performed the entry. This may take the form of an audit trail maintained internally by software, or may take the simple form of a log-in sheet on which staff members record their session with the electronic record system and identify what data was entered in that session.

**Evidence:**

The inspector will determine the scope of electronic records used by the CBB and any circumstances where the electronic record is used in lieu of a paper record.

While details of the validation system may be located in an institutional department of information services or elsewhere, the CBB shall have a summary of the validation available to the inspector.

If electronic records are used in addition to paper records, the inspector will evaluate the electronic record system to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system limits access to authorized individuals and that documentation is generated to identify which individuals have accessed the system and made record entries.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.



- Documentation that the individuals performing the development, maintenance, or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- Procedures are in place to provide for record keeping in the event of failure of the electronic record system, and that the staff members who may have to follow these procedures are trained in their use.
- A process for generating back-ups of records maintained electronically is in place.

**Example(s):**

When computers are used to generate paper printouts of electronic records, and the printouts are the “official” records used for the performance of further activities, the electronic records are not considered to be used in lieu of paper records. For example, an electronic record of the location of a CB unit in liquid nitrogen storage is printed for the unit record and the information is verified by a signature or initials. This printed record is then used by personnel to retrieve the unit at the time of infusion. The electronic record is not considered to have been used in lieu of a paper record, and may not be critical based on that criterion. If, however, the electronic system performed one or more calculations on the entered data prior to making the final printout, then the system is critical, and the standards in this section would apply. Similarly, if the electronic system formats data that is entered into a specific format for printing for retention, then that data is also processed, and validation that the data is being correctly reproduced is necessary.

For example, if a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a CB unit would not be directly affected. However, if a computerized system is used to make a critical calculation (e.g., CD34 cell recovery) and the electronic calculation is the only calculation performed, validation is required to assure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., when electronic records are used in lieu of paper, the inspector should refer to the FDA document Part 11, Electronic Records; Electronic Signatures - Scope and Application, for guidance to assess the validation procedures (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf>).

**STANDARD:**

**B12**      *INTERRUPTION OF OPERATIONS AT ESTABLISHED SITES*

*B12.1      In the event that any CB collection or processing function is discontinued for a period exceeding six months, there shall be documentation of the training and continued competency of all staff to perform the duties assigned upon resumption of activities.*

*B12.2      If CB collection activity is discontinued at any fixed CB Collection Site for a period exceeding six months, the CBB Director or designee shall review and renew the CB collection contract with that site.*

**Explanation:**

This standard applies to fixed CB Collection Sites and CB Processing Facilities that are a part of a FACT-accredited CBB. It is not applicable to non-fixed CB Collection Sites that collect related or unrelated CB units. These collecting health care professionals must, however, demonstrate an understanding of their participation in acquiring a CB unit.

**STANDARD:**

- B12.3 If a CBB discontinues processing of new CB units:*
- B12.3.1 There shall be competent staff to oversee, maintain, and distribute the inventory.*
- B12.3.1.1 The staff shall maintain communication with all relevant registries and Clinical Programs, if applicable.*
- B12.3.2 A process to distribute CB unit contiguous segments and samples for testing shall be maintained.*
- B12.3.3 All records of the entire inventory in storage shall be maintained.*
- B12.4 Prior to the reestablishment of either CB collection or processing, as applicable, the following at a minimum shall be documented:*
- B12.4.1 Review of all procedures to confirm that methods are consistent with current practices.*
- B12.4.2 Inspection of all reagents and supplies to confirm none will be used past its expiration date.*
- B12.4.3 Validation, calibration, and maintenance of all equipment have been completed within the time periods specified in the Standard Operating Procedures and manufacturer's instructions.*

**Explanation:**

CBBs must verify that their processes, supplies and reagents, and equipment comply with cGMPs and/or cGTPs as required prior to reestablishing operations.

**STANDARD:**

- B12.5 Cessation of operations.*
- B12.5.1 The CBB shall follow all contractual obligations that are specified in written agreements with CB Collection Sites, donor families, registries, and other entities.*

**Explanation:**

Operations must be discontinued in a manner that provides for the safety of inventory in order to maintain CB unit potency. CBBs that receive inventory from CBBs that cease operations are expected to follow the Standards related to transfer of inventory (B10), records (B11), etc.

DRAFT

## **PART C: CORD BLOOD DONOR MANAGEMENT AND COLLECTION STANDARDS**

### **STANDARD:**

#### **C1 GENERAL REQUIREMENTS**

*C1.1 These Standards shall apply to all CB donor management and collection procedures.*

#### **Explanation:**

CBBs have multiple relationships with CB Collection Sites and many approaches exist. No matter how the relationship between a CBB and CB Collection Site(s) is arranged, the Standards in C1 apply to all CB donor management and collection procedures.

The CBB applying for accreditation is responsible for ensuring that all aspects of donor management and collection, no matter where these activities take place, are in compliance with these Standards.

#### **Evidence:**

The CBB should be prepared to show the inspector contractual agreements for all sites and the organizational chart of the CBB with descriptions of the relationships, responsibilities, and roles of all facilities and personnel.

#### **Example(s):**

A CB Collection site may be in a maternity unit in a hospital, a birthing clinic, or in a home environment. The collection service may be staffed entirely by employees of the CBB, by health care professionals of the maternity unit/birthing clinic, or a mix of both.

A CB Collection Site may use a combination of physicians, midwives, nurses, and CBB staff to perform some or all of the activities involved in recruitment, consent, collection, donor selection, and donor screening. Training records and competency monitoring must be available for all staff participating in the activities.

**Figure 5: Cord Blood Collection Models** outlines the various methods by which collection activities may be arranged. All of the scenarios in this table must meet these Standards.

Figure 5: Cord Blood Collection Models

Site	Contract/ Agreement with	Donation initiated by	Type of CB unit		Collection model			Reagents & Supplies provided by			Staffing of Site						Training methods provided by CBB			
			unrelated	related	in-utero	ex-utero	in-utero + ex-utero	hospital	CBB		Collection responsibility			Shipping responsibility			observation	hands -on	competency	presentation
									individual supplies for collection activities	prepared collection kits	OB/midwife	hospital - phlebotomist/nurse/ research	CBB staff	OB/midwife	hospital staff - phlebotomist/nurse/ research	CBB staff				
Fixed	collection site hospital	CBB	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fixed	donor mother	donor mother		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fixed	donor mother	physician looking after sick-child		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fixed	Physician	donor mother	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fixed	Physician's group	physician's group	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-Fixed	donor mother	donor mother	X	X	X				X	X	X		X	X		X				X
Non-Fixed	donor mother	physician looking after sick-child		X	X				X	X	X		X	X		X				X
Non-Fixed	Physician	donor mother	X	X	X				X	X	X		X	X		X				X
Non-Fixed	Physician's group	physician's group	X	X	X		X	X	X	X	X		X	X		X				X

**STANDARD:****C1.2** *Written Agreements.*

- C1.2.1** *There shall be a written agreement specifying the relationship between the CBB and the CB Collection Site and outlining responsibilities for complying with CBB policies and Standard Operating Procedures.*

**Explanation:**

The written agreement for collection must specify not only the requirements for the collection and related procedures, but also who is responsible for them. These Standards do not dictate precisely whom the CBB must have an agreement with given the different cord blood collection models in use.

Even though responsibilities for CB collection, labeling, and transport or shipping for unrelated donations at non-fixed sites are given to the donor's family and the collecting health care professional, the CBB is obligated to document that the CB Collection Site and all responsible parties follow the CBB policies and procedures related to the collection of CB. See B3 and C3 for a list of all required policies and SOPs required for CB collection.

For collections at non-fixed sites where the contract may only involve the CBB and family, there should be an obvious mechanism of education and expectations communicated to the collecting health care professional. In addition to policies, SOPs, and instructions for collection, programs involved must also engage parents by providing materials with clear instructions and responsibilities.

Agreements referred to in this standard include administrative aspects such as scope of responsibility and understanding of participation, as well as technical aspects such as method of collection and length of storage. There must also be evidence of CB Collection Site compliance with CBB policies and SOPs related to donor selection and screening, collection staff training, performance of collection, and transportation and shipment to the CBB.

**Evidence:**

Inspectors will review agreements for inclusion of appropriate procedures and responsibilities that are required. The written agreements should include:

- Clear descriptions of roles and responsibilities,
- Training requirements, and
- Audits.

There must be documentation that a health care professional has agreed to perform the collection. This could be in the form of signatures (printed or electronic), training, etc.

Documentation of written agreements will usually be at the CBB rather than at the CB Collection Sites. The inspection team will need to coordinate responsibilities for reviewing these agreements.

**Example(s):**

Written agreements for CB donor management and collection at fixed CB Collection Sites are usually between the CBB and the fixed site. The agreement for related donations is typically between the CBB and the family, not with the CB Collection Site.

For unrelated donations at non-fixed sites, the agreement may be between the health care professional and the CBB or between the donor mother and the CBB. Generally, the infant donor's mother initiates the process for collection of unrelated CB units at non-fixed sites and works with the health care professional to confirm he/she meets elements in the written agreement. If this is the case, the CBB should include this in the instructions sent to the infant donor's mother.

Typically, the donor family is responsible for enrollment, providing medical history, and transport or shipping. Health care providers must be responsible for training and performing the CB collection procedure in accordance with the CBB policies and procedures.

Written agreements and informed consent documents can be organized in many ways; for example, collections at non-fixed sites may include the written agreement and informed consent in a single document. CBBs can organize the information in varying ways as long as all of the required elements are included.

**STANDARD:**

*C1.2.2 There shall be documentation that a health care professional has agreed to perform the collection.*

**Explanation:**

Depending on the collection model used by the CBB, this documentation may arrive at the CB Processing Facility with the collected CB unit.

**STANDARD:**

*C1.3 CB Collection Sites.*

**Explanation:**

CBBs may have fixed and/or non-fixed CB Collection Sites. A fixed site is a site where there is a written agreement between the CBB and the CB Collection Site that is in effect over a period of time for all CB donor management and/or collection procedures (as specified in the agreement). A non-fixed CB Collection Site is a site where the agreement is specific to the donor management and/or collection of a single CB unit.

**Example(s):**

CB Collection Sites may be hospital units, birthing centers, homes, etc. No matter where the CB Collection Site is, it must comply with these Standards.

**STANDARD:**

*C1.3.1 The CB Collection Site shall have processes to prevent the introduction, transmission, or spread of communicable disease.*

**Explanation:**

It is understood that CB collection is not free of contamination; however, the CB Collection Site's methods must not introduce additional contamination or transmit or spread communicable disease.

**Evidence:**

Inspectors may verify compliance to this standard by the following:

- Policies and procedures for cleaning and disinfection,
- Personnel screening and use of personal protective equipment,
- Segregation of bench, supplies, labels, technologists, etc. from one collection to another,
- One cord blood collection performed at a time,
- Records of cleaning and disinfection, and/or
- Tour of site and demonstration of procedures.

**Example(s):**

CBBs in the U.S. that collect CB units for unrelated allogeneic use must follow GMPs as a requirement for FDA licensure.

**STANDARD:**

*C1.3.2 There shall be adequate space for the performance of the collection procedure.*

**Explanation:**

The space used for collection of CB should be well defined and adequate. If other activities are performed on the equipment and in the space assigned at the CB Collection Site, concurrent activities must be performed in such a way as to not pose a risk of contamination or CB unit mix-up and must not adversely affect the integrity of the collected cells.

**Evidence:**

It is acceptable for the CB Collection Site to use the same space for CB collection and other activities, so long as the concurrent activities do not pose a risk of contamination, product mix-up, or adversely affect the integrity of the collected cells. There should be evidence of organized procedures and proper precautions against contamination.

**Example(s):**

The collection procedure may be performed on a cart, in the home with ample room for the supplies and collector, etc.

**STANDARD:**

*C1.3.3 There shall be adequate space for secure storage of the CB unit, associated samples and maternal samples, and documents until they are transported or shipped to the CB Processing Facility.*

**Explanation:**

A secure environment is one where the general public or unauthorized persons do not have access. CB units must be kept safe and free from tampering. Only authorized personnel should have access to CB units and associated documentation. A chain of custody needs to be established and documented.

**Evidence:**

There must be evidence that opportunity for tampering with the collected CB unit and its components is reasonably minimized. This could be verified with forms that trace the chain of custody of the unit or through other means by which the CBB documented the security of the unit.

**STANDARD:**

*C1.3.4 There shall be a designated area for appropriate and secure storage and preparation of the reagents, supplies, and equipment needed for the collection procedures.*

*C1.3.4.1 Reagents, supplies, and equipment shall be stored according to the manufacturer's recommendations in an area and manner appropriate to protect their integrity and functionality.*



*C1.3.4.2 The temperature of reagents and supplies in a CB collection kit shall be continuously monitored from the time it leaves the CBB to the time it is received by the CB Collection Site.*

*C1.3.4.3 Reagents and supplies shall be used prior to the expiration dates.*

**Explanation:**

This standard applies to supplies, reagents, and equipment at fixed CB Collection Sites and to the shipment and storage of collection kits. Patient care areas are designed to maintain an environment that is comfortable for staff and patients and thus are kept within a limited temperature range, but the inventory of supplies and reagents must also be stored according to manufacturer's recommendations in a way that protects their integrity. Conditions such as temperature and humidity during storage at collection sites and shipment to remote and non-fixed sites can affect the quality of the reagents and supplies and in turn the quality of the collected CB unit.

**Evidence:**

If storage issues may negatively affect the integrity of supplies and reagents, such as if the supply or reagent is stored in direct sunlight on a window ledge or on a shelf under or over an illuminated light fixture, this will be noted in the inspection report.

The CBB should make available to the inspector records of temperature and humidity in storage areas. Data collected from monitoring kits sent to non-fixed CB Collection Sites from the time they leave the CBB to their return will provide important information for verifying compliance, as will comparison between the storage conditions and the manufacturer's recommendations.

Inspectors may also review information provided to donor mothers/physicians regarding storage of the kits before use.

Inspectors will review expiration dates on stored inventory and verify stock rotation. There should be documentation of inspection of supplies and reagents prior to use.

**Example(s):**

The following are methods that may be used to confirm the temperature of storage areas is appropriate for supplies and reagents:

- Temperature monitoring records for storage areas, with evidence of review of records and follow up of excursions outside of the documented acceptable ranges.
- Printouts from data loggers from non-fixed site collection kits to confirm temperature range acceptable for supplies and reagents during the storage time prior to the CB collection and acceptable for the CB during return.

**STANDARD:**

*C1.4 When a CB collection kit is prepared and sent from the CBB, there shall be adequate instructions and materials provided to collect, label, store, pack, and transport or ship the reagents and supplies, CB unit, associated samples, and maternal samples.*

*C1.5 Records supplied to the CBB shall include the following at a minimum:*

*C1.5.1 Identity of supplies and reagents including manufacturer, lot number, and expiration date.*

**Explanation:**

A variety of approaches are employed by CBBs for the acquisition and tracking of supplies and reagents. If collection supplies are furnished by the CB Collection Site, appropriate information, such as lot number, manufacturer, and expiration date, must be recorded and provided to the CBB. Any supplemental supplies added to a collection kit at the CB Collection Site should be documented. There should be a distinction between “critical supplies” and other type of supplies. The CBB should define what it specifically considers as “critical supplies.”

**Evidence:**

There should be documentation that permits the tracking and tracing of supplies and reagents to the CB unit.

The inspector should be provided documentation that verifies the use of reagents and supplies prior to the expiration dates. Where kits are provided by the CBB to a CB Collection Site, there must be a process by which the collection site personnel can confirm that the reagents and supplies have not expired.

**Example(s):**

In some CBBs, the central facility controls the collection supply inventory, and assumes responsibility for recording lot numbers and expiration dates of components in the kit. This documentation is likely retained by the central facility and need not be kept at the CB Collection Site. Consideration should be given to recording lot numbers and expiry dates in such a manner as to facilitate a recall and/or investigation, as required.

**STANDARD:**

*C1.5.2 Documentation of appropriate storage of all supplies, reagents, CB units, associated samples, and maternal samples.*

**Explanation:**

Many reagents and supplies have specified storage temperatures. CB units, reference samples and maternal blood samples will be stored within defined environmental conditions to maintain their viability.

**Evidence:**

The inspector should look for environmental/temperature logs of storage areas for reagents and supplies, CB units, reference samples and maternal blood samples.

**Example(s):**

One approach to complying with this standard would include recording the temperature of the area where kits are stored. This could be accomplished by:

- Appropriate documentation of temperature readings or min/max thermometers, or
- Use of data loggers.

**STANDARD:**

*C2 CORD BLOOD COLLECTION PERSONNEL REQUIREMENTS*

*C2.1 All CB collection personnel shall comply with these Standards.*

**Explanation:**

It is the responsibility of the CBB to provide or confirm that collection personnel have adequate training to perform CB collection procedures, and to have adequate numbers of trained personnel available for the collection of CB relative to the workload. Therefore, all of the personnel requirements in B1 are applicable to CB Collection Sites, which includes personnel not employed by the CBB.

The number of staff available and responsibilities of the staff will vary from institution to institution and no specific numbers of staff members are required by these Standards.

It is understood that the contract in related banking programs is often between the family and CBB, not the CB Collection Site. However, this does not remove the obligation of the CBB to assure the training and competency of the health care professional to achieve the highest quality collection for their customers.

**Evidence:**

The CBB, as well as the inspection team, will make a judgment of the adequacy of the staff support. Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

If health care professionals not employed by the CBB are involved in the collection process (such as obstetricians, midwives, etc.), it is expected that there will be evidence of their training and knowledge of the applicable CBB policies and SOPs.

**STANDARD:**

- C2.1.1 Where there are CB Collection Sites that are not staffed by CBB personnel, there shall be a designated individual who is responsible for communication with the CBB Medical Director or designee.*
- C2.2 All CB collection personnel shall have a defined line of communication with relevant CBB personnel.*
- C2.2.1 At non-fixed CB Collection Sites, the CBB shall provide a mechanism for the collecting health care professional to communicate with the CBB Medical Director or designee for any problems with the collection.*

**Explanation:**

At CB Collection Sites where individual health care professionals perform collections, the individual performing the collection may serve as the contact person.

**Example(s):**

CBBs with fixed CB Collection Sites can provide collecting health care professionals a copy of the organizational chart of the CBB.

**STANDARD:**

- C2.3 All collections shall be performed by health care professionals trained for the collection procedure.*
- C2.3.1 Training shall cover each aspect of the CB collection process, and include at a minimum:*
  - C2.3.1.1 The use of the collection supplies and reagents.*
  - C2.3.1.2 Cleaning of the umbilical cord to minimize the risk of microbial contamination with maternal blood.*

*C2.3.1.3 Use of the CB collection bag to avoid microbial contamination and clotting.*

*C2.3.1.4 Labeling.*

*C2.3.1.5 Verification of the identity of the donor.*

*C2.3.1.6 Packaging, storage, and shipping of the CB unit.*

*C2.3.1.7 Safety of the donor mother and infant.*

*C2.3.2 Training shall be documented.*

**Explanation:**

Collection personnel, whether employed by the bank or not, must have training in key tasks, and initial and ongoing competency and training must be documented.

**Example(s):**

There are many approaches to collection methods and distribution of the responsibilities involved with collection. Activities may be solely performed by CBB personnel. Alternatively, maternal screening and eligibility may be performed by nursing personnel with the collection by a health care professional.

Training of collecting health care professionals can be accomplished by a variety of means, such as video or web-based presentations, with or without questions to assess knowledge gained from the training, followed by acknowledgement by the health care professional of his/her understanding of the principle elements of collection.

**STANDARD:**

**C3** *POLICIES AND STANDARD OPERATING PROCEDURES*

*C3.1 The CB Collection Site shall establish and maintain policies and/or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B2. These documents shall include all elements required by these Standards, be consistent with the policies and Standard Operating Procedures of the CBB, and address at a minimum:*

**Explanation:**

The standards in B2 and B3, including those related to policies and SOPs, apply to CB Collection Sites. CB Collection Sites' policies and SOPs must comply with those standards and address all elements listed in C3.3.

**Evidence:**

Given the wide variety of practices in CBBs, each CBB and its individual CB Collection Sites may have different policies and procedures that satisfy FACT requirements. The CBB must therefore explain to the inspector, via pre-inspection documentation and on-site demonstration, the collection approach utilized by the particular CBB, how all components are captured in its SOPs, and that the practices are followed at each of the CB Collection Sites. This applies to both fixed and non-fixed CB Collection Sites.

It will facilitate the inspection process if the CBB creates a crosswalk between the elements required in C3.3 and its SOPs.

**Example(s):**

The CBB may address multiple concepts listed in C3.3 in a single SOP, or address one concept in multiple SOPs. This is acceptable so long as all elements are included somewhere in the CB Collection Site's SOPs.

**STANDARD:**

*C3.1.1 Donor recruitment and education.*

*C3.1.2 Maternal screening (including interpretation and acceptable results).*

*C3.1.3 Informed consent.*

**Example(s):**

In some instances, persons other than the mother are required to provide consent. This must be reflected in the consent process, when applicable.

**STANDARD:**

*C3.1.4 Donor eligibility criteria.*

**Explanation:**

SOPs regarding maternal and infant donor screening and eligibility criteria are required; however, they may be applied after the CB unit has arrived at the CB Processing Facility. SOPs must outline who performs the screening and when, and detail what the screening includes, how the results are interpreted, and what results are acceptable.

The CBB must document donor eligibility criteria and acceptable results. Donor eligibility must be determined for each CB unit.

**Example(s):**

CBBs may have policies for automatic deferrals before collection is performed, and/or all donor eligibility determination may be made at the time the CB unit arrives to the CB Processing Facility.

**STANDARD:**

*C3.1.5 Documentation of infant donor health at birth.*

*C3.1.6 Infant donor screening.*

**Explanation:**

CBBs must document the process for infant donor screening similar to the maternal process. This includes interpreting the results obtained from the review of medical records.

**STANDARD:**

*C3.1.7 Maintenance of linkage of the CB unit to the infant donor and mother.*

*C3.1.8 Collection of CB, associated samples, and maternal samples.*

**Explanation:**

Most CBBs create reference samples from aliquots of the CB unit upon arrival to the CB Processing Facility; however, some CB Collection Sites may collect associated samples from the CB unit, umbilical cord, or placenta at the time of delivery. These Standards were written to include associated samples for these situations.

**STANDARD:**

- C3.1.9 *Labeling of the CB unit, associated samples, maternal samples, and associated documents.*
- C3.1.10 *Storage and packaging of CB units, associated samples, maternal samples, and documentation at the CB Collection Site.*
- C3.1.11 *Transport and shipping of the CB unit, associated samples, maternal samples, and documentation to the CB Processing Facility.*
- C3.1.12 *Personnel and collector training.*
  - C3.1.12.1 *Documentation of continued competency, if appropriate, for the procedures performed.*
- C3.1.13 *Ordering, storage, security, and use of supplies and reagents.*
- C3.1.14 *Equipment monitoring, qualification, and maintenance.*
- C3.1.15 *Facility management including cleaning and sanitation procedures, disposal of medical and biohazardous waste, emergency and safety procedures, and a disaster plan.*

**Explanation:**

The disaster plan can include the larger institution's disaster plan, but the CBB must address specifically the needs of the CBB.

**Evidence:**

Examples of policies and SOPs that have been revised with appropriate signatures and documentation of training should be noted during inspection; this is especially important in CBBs where the central CBB manages separate CB Collection Sites.

Procedures for disposition of biohazard waste should be available. If this task is contracted with an external company, minimal qualifications for the company as well as the contract should be available during the inspection.

**Example(s):**

The disaster plan may include key CBB personnel that must be contacted, a flow chart for maintaining operations (if possible), etc.

**STANDARD:**

- C3.2 *All collection personnel shall follow the policies and Standard Operating Procedures related to their positions established by the CBB and the CB Collection Site.*

**Explanation:**

The intent of this standard is to require that all policies and SOPs related and relevant to the collection of the CB unit are followed. The CBB is responsible for verifying that CB Collection Sites' SOPs are appropriate for the collection of CB.

**Evidence:**

The key policies and SOPs should be at all sites.

**Example(s):**

Most SOPs should be created by the CBB itself. However, some SOPs may be created by the individual CB Collection Sites as they may apply only for the site, such as facility cleaning sanitation and hours of operation.

**STANDARD:**

- C3.2.1 *Current versions of the policies and Standard Operating Procedures relevant to the processes being performed shall be readily available to the personnel involved in the CB collection procedures at all times.*
- C3.2.2 *Review and training of an individual participating in CB collection shall be documented before the individual is allowed to perform new and revised policies and procedures.*

**Explanation:**

“Readily available” means that the SOP is present in the area where the procedure is performed and everyone who performs the procedure has access to it. Policies and SOPs may be available electronically, given that a method to access them is available at all times, even in power failure. All the personnel involved in the SOPs described in C3 must have permanent access to these procedures.

**Evidence:**

Procedures available at the time of inspection must be the ones currently in use, whether available electronically or in conventional paper format. This must be proven by a system of versioning and distribution control. The procedures must be current (the latest version).

**Example(s):**

If the document tracking and management is not provided by the central CBB, there should be document tracking and management in place at the CB Collection Sites.

To provide non-fixed CB Collection Sites access to the policies and SOPs, a CBB may provide them in paper format or on a flash drive included in the collection kit.

Electronic access to policies and SOPs is acceptable; however, there must be a back-up plan for access to these documents when the electronic system fails. Back-up plans may be DVDs containing copies of the documents, power back-ups, and/or paper copies.

**STANDARD:**

**C4 INFORMED CONSENT**

*C4.1 Informed consent shall be obtained and documented from the mother.*

*C4.1.1 Informed consent shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.*

**Explanation:**

Most women present to the hospital for induction or in early stages of labor, allowing time for education to permit the informed consenting procedure. The potential donor must be alert, comfortable, and able to give informed consent and must not be distracted by pain or other labor activities. General or systemic anesthesia and sedation medications (such as diazepam, midazolam, or similar) must not have been administered prior to the consent process; however, an epidural is acceptable. The collection staff must determine the appropriate time to obtain the informed consent (information can be obtained by consulting with the mother's nurse).

Informed consent processes vary among CBBs. The Institute of Medicine publication, *Cord Blood, Establishing a National "Hematopoietic Stem Cell Bank Program,"* reports on the importance of obtaining informed consent for the donation of any CB unit, regardless of the timing of collection or its potential use. The report recognizes the practicality and demographic realities of the donor communities while emphasizing that informed consent procedures must be designed to protect the interests of the infant donor's family and educate the infant donor's mother about the various options for CB use. (Refer to pages 107-112 of the report.)

**Evidence:**

At a minimum, there needs to be documentation of fundamental knowledge of the collection (rationale and process) prior to the collection.

**Example(s):**

The United Kingdom Human Tissue Authority (HTA) published an updated Code of Practice on Consent in September 2009. This document can be found online at <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice/code1consent.cfm>.

Many acceptable strategies can be applied to obtaining consent, especially in regards to the timing of when consent for certain processes is obtained. Examples of different ways to comply include:

- Two-step process: pre-consent for collection followed by a full consent for obtaining health information and placing the unit into storage upon collection of an adequate CB unit. In this process, the pre-consent needs to include exactly what steps will be taken by the CBB before the full consent is obtained. The CBB must obtain full consent before the CB unit is placed into long-term storage. This process may be used when a mother presents to a fixed CB Collection Site while in active labor.
- Single-step consenting process: full consent administered prior to collection to permit all aspects of collection and banking. This process may often be easier because it is less dependent on the nature of the delivery (e.g., duration of time from admission to the hospital for delivery to the administration of sedating medication). This may be used for cases in which the mother and/or the fixed CB Collection Site initiates the donation process early in the pregnancy.

**STANDARD:**

*C4.1.2 In cases of a surrogate mother, informed consent shall be obtained and documented from both the surrogate mother and the genetic mother.*

*C4.2 All aspects of participation in CB donation shall be discussed with the mother in a language and with terms that she understands.*

**Explanation:**



A person who provides interpretation and/or translation must understand the collection, storage, and/or banking procedure, as applicable, sufficiently enough to explain the process adequately to the mother. The explanation of the procedures must be in a form that is understood by non-medical persons. If possible, the informed consent should be translated into the mother's native language.

**Evidence:**

The CB Collection Site should provide the inspector copies of consent forms in other languages and/or evidence of bilingual staff.

**Example(s):**

Mothers who do not speak the working language of the CB Collection Site should have materials available in their language. Alternatively, the materials may be interpreted through bilingual staff or a hospital interpreter and the activity documented. IRBs may require certain languages to be used routinely based upon the characteristics of the donor population.

**STANDARD:**

*C4.3 Informed consent shall be obtained from or confirmed by a trained individual who is not a member of the donor's family.*

*C4.4 The CBB shall only perform steps in the CB banking process for which it has informed consent from the mother, including at a minimum:*

*C4.4.1 Collection.*

*C4.4.2 Processing.*

*C4.4.3 Long-term storage.*

**Explanation:**

CBBs obtain informed consent in differing ways, most notably in the timeframes in which informed consent is obtained. These Standards do not prescribe how a CBB may choose to obtain consent for various steps in the CB banking process; however, only those steps that the mother has consented to can be performed.

The information that must be included in the consent process is listed in C4.6. It is the responsibility of the CBB that the relevant information is provided to the mother at the appropriate steps of the CBB's informed consent procedure.

**Example(s):**

If a CBB performs a "mini consent" before collection and then obtains full consent after the collection is verified to be of sufficient volume, the CBB must obtain informed consent for the collection procedure before collecting.

**STANDARD:**

*C4.5 The mother shall have an opportunity to ask questions.*

**Explanation:**

The willingness to donate CB must be an individual choice of the mother. She must have the opportunity to ask questions that clarify the process of collection and donation and be free to withdraw at any time.

**STANDARDS:**

*C4.6 The informed consent shall include the following information at a minimum:*

- C4.6.1 The overall purpose and participation of the mother and infant donor.*
- C4.6.2 An explanation of the collection procedure and activities in terms the mother can understand.*
- C4.6.3 The possible risks and benefits to the mother and/or infant donor.*

**Explanation:**

The explanation of the collection procedure should include the possible risks and benefits of CB collection.

**STANDARD:**

- C4.6.4 The possible alternatives to participation.*
- C4.6.5 The right of the mother to refuse without prejudice.*
- C4.6.6 The intent of the donation for either unrelated use or for related use.*
  - C4.6.6.1 If the CB unit is intended for unrelated use, the mother shall be informed that the CB unit is a donation that will be made available to other individuals and will not necessarily be available to the infant donor or the infant donor's family at a later date.*
  - C4.6.6.2 If the CB unit is intended for related use, the mother shall be informed that the release of the CB unit will be limited to the family, intended recipient(s), or the infant donor.*
  - C4.6.6.3 If the CB unit is intended for related use but may potentially be used for unrelated use, the mother shall be informed of the process for making the CB unit available for unrelated use.*
  - C4.6.6.4 If the CB unit may potentially be used for reasons other than the primary intent, this shall be fully disclosed in the informed consent.*

**Explanation:**

Use of related CB units must be clearly described in a CBB's procedure to avoid inadvertent release. Some CBBs utilize a model in which CB units originally collected for related use are subsequently released for unrelated transplantation. This model has considerable implications for informed consent, and the maternal donor must be informed that the CBB may choose to release the CB unit for unrelated administration if she chooses not to retain the CB unit for related use.

If a CBB utilizes this model, it must still meet all applicable requirements for unrelated CB units (including donor eligibility), even if it was originally collected for related use.

While the consent for collection may be obtained from a family member, the full consent cannot. Not only may family members not understand the procedures, they may present a conflict of interest in which the donor will not provide complete and truthful information.

**Example(s):**

The CB unit may be collected for related use, but then listed for unrelated use if the family no longer wishes to store the unit for its own use. Alternatively, a CB unit may be collected for unrelated use, but testing shows insufficient volume and the unit is used for research instead.

**STANDARD:**

*C4.6.7 The mother will be asked to provide personal and family medical history.*

*C4.6.8 Personnel will be permitted to review the medical records of the mother and infant donor.*

**Explanation:**

This standard requires inclusion of the language of this standard in the consent. Its purpose is to permit the CBB to review the infant donor's and its mother's medical records.

**STANDARD:**

*C4.6.9 Maternal samples and associated samples will be collected.*

*C4.6.9.1 A sample will be collected from the mother for communicable disease testing and other testing, as applicable.*

*C4.6.9.2 Associated samples and maternal samples will be collected for communicable disease testing, genetic disease testing, HLA typing, and other testing, as applicable.*

*C4.6.10 Associated samples, reference samples, and maternal samples will be stored for future testing.*

*C4.6.11 The CBB will indefinitely maintain linkage between the donor and the CB unit.*

**Explanation:**

As required by the CB unit testing standards, the CBB must have a mechanism for any abnormal findings to be reported to the infant donor's mother or physician.

**STANDARD:**

*C4.6.11.1 The CBB retains the right to follow up with the mother or relevant healthcare provider at a future date.*

**Explanation:**

The informed consent should make clear the possibility that the CBB could contact the infant donor's mother or relevant healthcare provider (e.g., the mother's physician, the infant donor's physician, etc.) at any time for follow up. This may include providing the infant donor's family information on CB unit test results (e.g., genetic disorder test results), or later when the CBB performs bank-initiated donor follow-up.

**Example(s):**

At some CBBs, it is the policy to contact the infant donor's family prior to release of the CB unit for transplant to update infant donor health screening.

**STANDARD:**

*C4.6.11.2 Information related to the infant donor and the infant donor's family shall remain confidential and is only available for review by individuals designated by the CBB or by national authorities to evaluate the CBB.*

**Explanation:**

In addition to health care professionals on a need-to-know basis to the extent allowed by Applicable Law, individuals designated by the CBB to review confidential information include accrediting agencies, external auditors, and other individuals the CBB may request to review the information for quality purposes.

**STANDARD:**

*C4.6.12 The CB unit will be processed, stored, and made available for use.*

*C4.6.12.1 Information regarding the CB unit, including donor eligibility, will be shared with registries nationally and/or internationally, as applicable, and with other individuals as appropriate.*

*C4.6.13 Possible uses of the CB unit for purposes other than clinical administration.*

**Example(s):**

Examples of possible uses of CB units other than clinical transplantation include research, quality control, or validation studies.

**STANDARD:**

*C4.6.14 The CBB's policies for disposal of CB units, including at a minimum:*

*C4.6.14.1 Nonconforming CB units.*

*C4.6.14.2 Related CB units, if these units are no longer required.*

*C4.6.14.3 Agreed-upon duration of storage for related CB units.*

**Example(s):**

There are many reasons why a CBB may choose to discard nonconforming CB units, such as those with cell counts or microbial contamination results that do not meet the bank's criteria, positive infectious disease markers, etc.

**STANDARD:**

**C5 MATERNAL AND INFANT DONOR EVALUATION**

*C5.1 There shall be written criteria for maternal and infant donor evaluation and management.*

*C5.1.1 There shall be a process for maternal and infant donor identification and linkage.*

*C5.1.2 There shall be criteria and evaluation procedures in place to protect the safety and confidentiality of the infant donor and mother.*

- C5.1.3 *If a related CB unit may potentially be used for unrelated donation, the evaluation process shall include all evaluation requirements for unrelated CB units at the time of donation.*
- C5.1.4 *Maternal and infant donor evaluation results shall be documented.*
- C5.1.5 *Maternal and infant donor evaluation shall be reviewed by qualified CBB personnel.*

**Explanation:**

Donor suitability refers to the maternal and infant donor's medical fitness for the CB collection procedure. A CBB or CB Collection Site staff member who is not licensed may have sufficient knowledge to perform the initial evaluation of the donor; however, the final review of the evaluation data and decision on whether or not the maternal and infant donors are suitable for the procedure must be made by qualified CBB personnel. These personnel members must confirm the answers are consistent, obtained correctly, and do not indicate risks to the donors and/or CB unit.

**Example(s):**

Situations in which a donor may not be suitable for the CB collection procedure include a baby with a gestational age of less than 33 weeks or a maternal donor with delivery complications requiring medical assistance that would be interfered with by collection.

**STANDARD:**

- C5.1.6 *There shall be a policy for follow-up of donors for management of donation-associated adverse events.*

**Explanation:**

This standard requires that the CBB has in place written SOPs defining all aspects of infant donor identification, evaluation, selection, and management. This standard is intended to promote the safety of the donor and recipient as well as the safety and efficacy of the stem cell product. While it is recognized that adverse events are highly unlikely for *ex utero* collections, all maternal and infant donors shall be evaluated for donation-associated adverse events (for example, needle stick injuries). Any adverse events need to be documented.

The standard does not define an acceptable donor. Instead, it requires that the CBB define the institutional criteria for donor selection. It also requires that each aspect of this process be performed according to written SOPs and the results of the evaluation be documented.

**Evidence:**

Policies and SOPs for donor selection must be written, clearly defined, and unambiguous. Compliance with these SOPs may be verified by reviewing a specific donor evaluation.

**STANDARD:**

- C5.2 *There shall be infant donor and mother evaluation procedures in place to evaluate the risk of infectious and genetic disease transmission from CB units.*

- C5.2.1 *Maternal and infant donor eligibility shall be determined based upon results of screening and testing in accordance with Applicable Law.*

C5.2.2 *Risks of genetic disease transmission shall be determined based upon results of the screening questionnaire and testing.*

**Explanation:**

These donor evaluation criteria must meet all applicable local and national laws. International laws may also apply. The CBB is not expected to perform genetic testing, but obtain the history of genetic testing of the infant and maternal donors from the donor family.

**Example(s):**

CBBs that import CB units into the U.S. are subject to U.S. regulations. More information for the U.S. can be found in the FDA's Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm>.

The HTA "Guidance document for establishments working with Umbilical cord blood" (November 2010) states that the CBB should have a policy on what steps would be taken if a CB unit stored for autologous use and meeting only requirements for autologous testing was requested to be released on an allogeneic basis. This document can be found at [http://www.hta.gov.uk/\\_db/\\_documents/Cord\\_Blood\\_Guidance\\_Document.pdf](http://www.hta.gov.uk/_db/_documents/Cord_Blood_Guidance_Document.pdf).

**STANDARD:**

C5.3 *There shall be written criteria for maternal screening.*

C5.3.1 *A medical and genetic history of the infant donor's family (parents, grandparents, siblings, and parents' siblings including egg, sperm, or embryo donor, if applicable) shall be obtained from the maternal donor and documented.*

C5.3.1.1 *The history shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.*

C5.3.1.2 *The history shall be obtained in a language the mother understands.*

C5.3.1.3 *Family members should not serve as interpreters or translators.*

**Explanation:**

If the mother does not understand the language of the personnel collecting the history, someone with sufficient training and understanding to accurately translate and/or interpret the questionnaire and information must obtain the history. The use of family members to translate and/or interpret the medical history procedure is not recommended due to the risks of the mother withholding information for privacy concerns and due to a family member's possible lack of understanding of the procedure.

**Example(s):**

Methods to collect medical and genetic history include in-person discussions, forms with follow-up by the CBB, telephone interviews, etc.

**STANDARD:**

*C5.3.1.4 The history shall collect information to include at a minimum genetic history, malignant disease, and inherited disorders that are transmissible to the recipient in the mother's and father's family including the infant donor's grandparents, if known.*

**Explanation:**

Genetic history refers to the donor evaluation tool designed to elicit information about the family's hematopoietic, immunologic, and metabolic disease history. Medical screening of the genetic parents, i.e., those persons supplying the genetic material through sperm or egg that determines heredity in a new individual, is required to assess risks of diseases and conditions that may be inherited through the material that contributed to the genetic makeup of the infant. The donor family may not know the information, but CBBs are expected to attempt to obtain this information.

Genetic history should include questions screening for metabolic disorders such as Tay Sachs (for the purpose of avoiding transplant of CB from an affected donor in the setting of treatment for that specific disease) or disorders of the blood and immune system (e.g., sickle cell disease, thalassemia, and immunodeficiency syndromes). The genetic history can also include ethnicity.

Medical history will elicit information such as leukemia and other cancers or auto-immune diseases in first degree relatives.

The CBB must attempt to elicit information regarding all of the parties named in this standard but it does not necessitate exclusion of the CB unit if history cannot be obtained, for instance, from a deceased grandparent, absent father, or where parents have been adopted. In these cases, the CBB should inform the Clinical Program at the time of release for administration.

**STANDARD:**

*C5.3.1.5 The CBB shall have policies to assess deferral of a donor or collected CB unit from unrelated allogeneic use if there is a family history of a genetic or malignant disease that could transmit to a recipient unless testing or follow-up excludes the risks.*

**Explanation:**

The CBB policies and SOPs must require that CB units are evaluated for the potential of inherited disorders and/or history of disease that may be transmissible, and must also specify when CB units deemed positive for these risks should not be kept in inventory in the unrelated allogeneic setting if testing or follow-up do not exclude the risks. CBBs may be in a jurisdiction in which Applicable Law defines when a unit must be deferred.

The CBB must determine acceptability of genetic conditions based upon available testing or possibility of follow-up for reasonable assurance the CB unit will not transmit genetic diseases. The CB unit shall not be accepted if there is not acceptable follow-up or testing. CBBs must document their evaluation process in SOPs.

**Example(s):**

CBBs may defer all CB units with a risk of transmitting genetic diseases or have a decision tree with certain criteria for acceptance or deferral.

The type of malignant diseases applicable to a CB donor varies around the world.

**STANDARD:**

C5.3.2 *A history for the mother's communicable disease risk behavior shall be obtained and documented.*

C5.3.2.1 *The mother's communicable disease risk behavior shall be obtained in a confidential manner.*

C5.3.2.2 *The history shall include the mother's prenatal communicable disease testing, if known, and results of other general medical testing that could influence communicable disease transmission.*

**Explanation:**

The rationale for requiring infectious disease and high-risk behavior history on the birth mother is driven by the fact that the woman carrying the infant shares circulation and, consequently, blood and body fluids through which infectious agents may be transmitted. History of potentially blood transmissible diseases must be obtained from the mother, tracked with the CB unit, and released to the Clinical Program.

**STANDARD:**

C5.3.2.3 *If history for communicable disease risk was obtained in advance of the maternal donor's presentation for delivery, the history shall be updated to include information up to the time of delivery.*

**Explanation:**

This standard applies to CBBs that educate and screen donors early in pregnancy (six months prior to delivery) to determine eligibility for participation. Upon delivery or soon thereafter, information previously provided during screening must be verified, including any changes to infectious risk history that may have occurred since the time of completion of the initial screening process. In addition to the health questionnaire, any other types of illness or conditions at the time of delivery, such as fever, that may impact the quality of the CB unit needs to be included in the history.

**Example(s):**

According to FDA 21 CFR part 1271, a full high-risk health history questionnaire must be performed within the last 6 months and at least an abbreviated high-risk health history questionnaire including review of the full high-risk health history questionnaire and a question to ask the donor of any changes must be completed.

Some CBBs may have a policy to perform follow-up calls to maximize capture of local risk factors, for example, demonstration of disease with lengthy incubation periods in areas where WNV, SARS, or malaria is prevalent. Most CBBs find that information obtained through this activity relates to manifestation of genetic diseases in the infant not immediately detected at birth.

**STANDARD:**

C5.3.2.4 *In the case of a surrogate mother who gives birth to an infant donor not genetically hers, a communicable disease risk history of the surrogate mother shall be obtained and documented.*

C5.3.2.5 *The mother's and surrogate mother's, if applicable, travel history shall be obtained and documented. Travel-related donor eligibility shall be determined according to Applicable Law and documented.*



*C5.3.2.6 In the case of sperm, egg, or embryo donation from a bank not licensed in accordance with Applicable Law, the communicable disease risk history of the sperm, egg, or embryo donor shall be obtained, reviewed, and documented.*

**Explanation:**

Because the medical and genetic history of egg and sperm donors impacts the risks of a CB unit, it is recommended that CBBs only accept into inventory CB units for which the donors' medical and genetic history has been collected. In most cases, this history would be obtained by the egg or sperm bank, and the actual documentation does not need to be at the CBB if the egg or sperm bank is accredited and/or licensed by the relevant regulatory agency.

If no genetic history is available for these donors, it is recommended that unrelated allogeneic donation be deferred to eliminate risk of transferring genetic or inherited disorders.

**STANDARD:**

*C5.3.2.7 Screening for human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease, shall be documented.*

**Explanation:**

CBBs are not required to test for Creutzfeldt-Jakob disease, but must ask questions to obtain information regarding any history of this disease.

**STANDARD:**

*C5.3.3 There shall be documentation that the mother and surrogate mother, if applicable, affirmed that all the information provided is accurate to the best of her knowledge.*

*C5.3.4 The CBB shall have policies regarding the acceptance of ineligible CB units for unrelated allogeneic use if there is a communicable disease risk.*

**Explanation:**

It is important to collect the maternal travel history. Travel history may impact banking or administration of CB units. CBBs should be familiar with applicable national disease center publications, including websites, for current travel restrictions and agents associated with travel. Travel restrictions do not necessarily exclude donors but may require special labeling and release documentation in accordance with current local and national laws.

HIV and hepatitis B transmission through high-risk behavior, such as intravenous drug use, incarceration, and prostitution, are well documented. CBBs must determine the necessity of including such CB units into the inventory and appropriately label and document the CB unit as ineligible, regardless of infectious disease testing results. CB units with a maternal high-risk behavior that exposes a potential recipient to a risk of HIV or hepatitis transmission must be deferred.

HIV-1 Group O is a communicable disease threat to inhabitants of certain African countries. Currently, not all test kits include tests that detect HIV-1 Group O.

**Example(s):**

Eligibility based on travel history is expected to change over time. For example, the current FDA risk assignments identify a risk for contracting vCJD through ingestion of beef or through the blood of another who ate beef while in the UK. Conflicts in practice arise when cumulative travel or time on military bases to Europe or the UK defers an American CB donor but the importation of CB units collected from European donors into the U.S. is permissible with proper documentation. CBBs may choose to retain these CB units in quarantined storage and allow the transplant physician to accept risk, so long as the CB units are labeled as “ineligible” in compliance with FDA travel guidance and the urgent medical need process is followed.

A U.S. CBB or a CBB importing to the U.S. must ask the FDA African travel questions or test with an FDA approved, cleared, or licensed test kit for HIV-1 Group O. If both are completed, the test results override the questions.

**STANDARD:**

*C5.3.5 When a mother does not meet the established screening criteria, the CBB Medical Director and a representative from the QM Program shall document and maintain in the permanent record the nature of the variances and the rationale for inclusion of that CB unit.*

**Explanation:**

The criteria will include all those implied by, but not limited to, these Standards. This documentation must be available to trained personnel performing the medical history screening and CBB personnel. Although maternal screening is required of all CBBs, related CBBs may choose to store nonconforming CB units. CBBs must have a policy for such criteria and this must be available to those obtaining the medical history and CBB personnel.

**STANDARD:**

*C5.3.6 The mother shall be provided with information to contact the CBB if the infant donor later develops a serious disease.*

**Example(s):**

There are a variety of ways this can be accomplished: through a contact card, on a copy of consent forms, or in a CBB brochure given to the mother at donation, which may list examples of serious disorders that would prompt notification.

*C5.4 Any abnormal result relevant to the health of the maternal or infant donor shall be reported to the maternal donor or donor’s physician.*

**Explanation:**

Even if a CB unit is not collected, abnormal results must be reported to the maternal donor or her physician so that the appropriate follow-up may take place.

**STANDARD:**

*C5.5 Infant Donor Screening and Testing.*

*C5.5.1 History of the current pregnancy and delivery shall be obtained and reviewed.*

*C5.5.2 The infant donor's birth data shall be obtained and documented, including gender, gestational age, other results of clinical examination, and if the baby is free of any finding suggestive of disease potentially transmissible through administration of a CB unit.*

**Explanation:**

Clinical examination of the infant donor is performed to evaluate risk of genetic disease transmission as well as observation of any infectious process at the time of birth. This examination must be conducted by a licensed medical professional who would normally perform infant assessment after birth and may include, for example, evaluation for the following:

- Extra digits,
- Absent thumb, and/or
- Congenital defects.

If an infant donor is delivered to term, documentation does not need to list the actual gestational age; however, pre-term deliveries must include the gestational age for further review by the CBB in accordance with its policies and procedures.

**Example(s):**

This requirement may be fulfilled at a later follow-up with the infant donor (for example, a national CB policy of reexamination of the infant at six to twelve months post-delivery). CBBs may either document the actual gestational age or indicate that the gestational age was greater than or equal to 34 weeks, which is required by these Standards.

**STANDARD:**

*C5.6 Maternal Samples.*

*C5.6.1 Blood from the birth mother shall be obtained within seven (7) days before or after collection of the CB unit for communicable disease testing required in D11.1.*

**Explanation:**

Obtaining samples within seven days of CB collection is necessary because the samples and their test results serve as surrogates for the CB unit. This timeframe also limits the risk of failure to follow up with the mother and the scope for mix up of samples. SOPs should define when samples should be obtained.

**Evidence:**

A procedure shall exist that explains in detail how and when maternal samples are collected, stored, and documented. The records of a CB collection should demonstrate compliance with this procedure.

**STANDARD:**

*C5.6.2 A sufficient volume of blood from the birth mother shall be obtained to meet D5.3.1.*

*C5.6.3 A sufficient volume of blood from the genetic mother including egg donors, if possible, shall be obtained to meet D5.3.2.*

**C6 CORD BLOOD COLLECTION PROCEDURES**

- C6.1      *CB collection procedures and practices shall protect the mother and the infant donor and have no impact on obstetric practice or patient care.*

**Explanation:**

The health of the maternal and infant donors is paramount to CB collection. It is inferred that if mothers deliver in hospitals, then emergency care is available. However, if a collection occurs during a home delivery, the CBB must have a plan for prompt access to emergency medical care for the maternal and/or infant donor when appropriate.

**Evidence:**

Written agreements for collections at non-fixed CB Collection Sites must include that the site be able to provide access to emergency medical care for the maternal and/or infant donor when appropriate.

**Example(s):**

There should be two health care professionals attending each delivery, and a hospital should be within a reasonable distance to allow provision of care in emergency situations. There should be a procedure for health care professionals collecting during a home delivery to contact emergency medical services or the community alert system (such as '911' in the U.S.) when necessary.

**STANDARD:**

- C6.1.1      *Delivery practices shall not be modified in an attempt to increase CB unit volume.*
- C6.2      *When in utero CB collection is performed, there shall be additional safeguards in place to protect the safety of the mother and the infant donor.*
- C6.2.1      *In utero CB collections should only be performed from documented singleton deliveries.*
- C6.2.1.1      *If CB collection is performed in utero in a multiple gestation pregnancy, all infants shall be delivered before any CB collection begins.*
- C6.2.2      *In utero CB collections shall only occur in uncomplicated deliveries as determined by the licensed health care professional responsible for the delivery.*
- C6.2.3      *Unrelated CB units collected in utero shall only be obtained from infant donors after a minimum of 34 weeks' gestation.*
- C6.2.4      *Related CB units collected in utero at less than 34 weeks' gestation shall be based on an evaluation of infant donor safety by the licensed health care professional responsible for the delivery.*

**Explanation:**

CBB policy and practice should address the safety of mother and infant(s). There are risks unique to *in utero* collections that must be appreciated. It is expected that CB collection would not occur if there is any difficulty during delivery (e.g., excessive maternal bleeding, difficult delivery, fetal/newborn distress, and/or serious maternal medical problems). In general, multiple deliveries are more complicated and the risk of misidentifying CB units is increased. Thus, *in utero* collections are not recommended in the unrelated donor setting.

There are also situations of an unexpected twin who may have a shared placenta with the first delivered infant. In these settings, *in utero* collection of CB could have a disastrous impact on the undelivered twin. Thus *in utero* collections should only occur in the setting of a known singleton delivery. Similarly if a CBB decides to collect from multiple gestation deliveries, then *in utero* collections should only be performed after all infants are delivered.

The standard requiring *in utero* CB collections after minimally 34 weeks gestation is because of a greater risk of a complicated delivery and because of the likelihood that the volume of collected blood would be low and not suitable for clinical use. However, *in utero* collection in a related setting is allowed so long as any issues involving the safety of the infant donor (e.g., resuscitation or other health issues) are prioritized.

**Evidence:**

Compliance with this standard may be verified using documentation from the collection and delivery.

**Example(s):**

Complicated delivery includes but is not limited to:

- Multiple births,
- Active sexually transmitted disease at the time of delivery,
- Blood transfusion during labor and delivery,
- Maternal temperature greater than 102° F or 38.9° C,
- Malodorous placenta,
- Excessive maternal bleeding, and/or
- Expulsion of placenta before or during collection.

**STANDARD:**

C6.3      *CB collection shall be performed according to written policies and Standard Operating Procedures.*

C6.3.1    *The identity of the mother shall be verified.*

C6.3.2    *The identity of the cord blood collector shall be documented.*

C6.3.3    *CB collection procedures shall be validated to result in acceptable progenitor cell viability, cell recovery, and rate of microbial contamination.*

**Explanation:**

There are many acceptable approaches and elements in validating CB collection processes. They must all show that the process is validated by establishing, by objective evidence, that the process consistently produces CB units with end points in a defined range; such as collected CB volume, nucleated cell counts, progenitor cells, cell viability, and microbial contamination.

**Evidence:**

Current versions of approved policies and procedures must be available to collecting personnel at the CB Collection Site.

If a procedure does not occur, or if it is not possible to observe an actual collection, the collection personnel should provide a verbal description. A mock collection procedure may be a useful tool to demonstrate the collection technique. For example, a verbal description of the procedure with some demonstration would demonstrate to the inspector that personnel follow the procedure and that the procedure meets the Standards.

Aseptic techniques should occur during a collection or mock collection. Microbial contamination rates should be trended and validated by the collector, CB Collection Site, or other categories as appropriate to the CBB, and corrective actions taken when necessary. In general, validation of the collection procedure would be inspected at the CBB where the quality activities are generally coordinated, performed, and analyzed, rather than at the individual CB Collection Sites. If an unusual collection technique is used, the procedure needs to demonstrate minimal maternal contamination.

**STANDARD:**

*C6.3.4 Methods for CB collection shall employ aseptic techniques.*

**Explanation:**

Aseptic technique is defined as practices designed to reduce the risk of microbial contamination of products, reagents, specimens, patients, or donors. Techniques include control of environment, equipment, personnel, and practices in a manner that precludes microbiological contamination of the exposed product.

**STANDARD:**

*C6.3.5 The CB collection bag shall be approved for use with human blood and sealed to prevent leakage and minimize the risk of cell loss and of microbial contamination.*

**Explanation:**

Most CBBs use blood collection bags that are currently on the market and already approved for use with human blood. The sealing process needs to be validated to prevent leakage.

**Evidence:**

The sealing process intended to “close” the system (e.g., tied, clamped, etc.) must demonstrate a proper seal. The CB Collection Site must also comply with the CBB’s policy regarding recapping needles (e.g., use of safety sheaths or one-handed “scoop” method) when disconnecting tubing containing a needle.

**Example(s):**

Examples of ways to close the system include the use of two clips, a clip and a knot, or two knots. Two seals are not required by the Standards if the CBB can demonstrate that its policy for sealing the bag is effective.

**STANDARD:**

*C6.3.6 All reagents and supplies for CB collection that come into contact with the CB unit shall be sterile.*

*C6.4 There shall be a unique numeric or alphanumeric identifier for the CB unit, associated samples, maternal samples, and associated documents.*

**Explanation:**

Unique refers to an identifier that is exclusive and distinctive and is not used for any other purpose. The essential point is that each CB donation, associated sample, reference sample, maternal sample, and associated document can be unambiguously traced from donor to recipient, and through all distribution and processing steps, and storage locations.

**Evidence:**

A review of identifiers used to track multiple steps should verify that a unique identifier is used and adequately links the CB unit, samples, and documents throughout the entire process.

**Example(s):**

At collection, the identifier may be a combination of the infant donor mother's first and last name, medical record number, and/or maternal birth date, and to be unique requires at least two such identifiers. This combination must be unique in the environment of the CB Collection Site. If temporarily used, these identifiers should not be observable by the courier or general public. Once received in the CB Processing Facility, this information can be associated with and provide linkage to a unique CB unit identifier that is assigned by the CBB.

**STANDARD:**

- C6.5 *There shall be a written policy at the CB Collection Site for labeling of the CB unit, associated samples, maternal samples, and associated documents that permits tracking and tracing among the CB unit, infant donor, infant donor's mother, associated samples, maternal samples, and documentation.*
- C6.6 *At completion of CB collection, the primary collection bag shall bear or be accompanied by the information required in the Cord Blood Unit Labeling table in Appendix I.*
- C6.7 *There shall be a written policy for storage of CB units, associated samples, maternal samples, and documents at the CB Collection Site prior to transport or shipping to the CB Processing Facility.*
  - C6.7.1 *CB units, associated samples, and maternal samples shall be maintained in a secure environment.*

**Explanation:**

A secure environment is one where the general public or unauthorized persons do not have access, and where opportunity for tampering with the collection and its components is reasonably minimized.

**Evidence:**

The labeling process must allow for proper identification and linkage of the CB unit, samples, and documents.

**Example(s):**

The CBB must have a process for assigning the correct maternal blood samples to the CB unit. There are many approaches to assuring this; one is to have two individuals verify the labeling and link between samples and CB unit.

**STANDARD:**

- C6.7.2 *CB units shall be maintained in a temperature range validated to protect cell viability.*

**Explanation:**

Many studies have been published to demonstrate the duration and effects of room temperature (20-24°C) storage on liquid CB collections. Whichever manner a CBB adopts, the process used must be validated either by the author(s) of the studies and/or the CBB and apparent to the inspector that it is used consistently (review of validation studies are observed by the CBB inspector and must be referenced in the applicable SOP when appropriate (see the policies and SOPs requirements in B3)).

**Evidence:**

One element of the validation is to evaluate storage of the CB units within a temperature range to maintain viability and potency during the required storage time at the CB Collection Site. CB units must be stored in an area where the appropriate temperature range is not negatively impacted by the environment, such as on a shelf in direct sunlight.

**Example(s):**

Examples of validating the temperature range during storage at the CB Collection Site include a) testing whether cells remain viable under extreme temperatures (especially high temperatures) experienced in storage areas or b) demonstrate that the storage area is climate-controlled and able to maintain reasonable temperature ranges. In this instance, monitoring the temperature of storage areas would be good evidence to demonstrate control.

**STANDARD:**

*C6.8 Records shall be maintained at the CBB of all reports of adverse events that occur during or immediately after CB collection.*

**Example(s):**

Records of adverse events may be maintained in the hospital but must be shared with the CBB for evaluation, trending, and possible corrective action. It is common that collection adverse events (for example, needle sticks) will be reported and managed by the hospital's employee health and/or risk management processes. The CBB must have a means to collect the frequency of such incidents within the CBB.

**STANDARD:**

*C7 TRANSPORTATION AND SHIPPING OF NON-CRYOPRESERVED CORD BLOOD UNITS BETWEEN THE CORD BLOOD COLLECTION SITE AND THE CORD BLOOD PROCESSING FACILITY*

*C7.1 Transport and shipping of CB units shall be in compliance with Applicable Law.*

*C7.2 The methods of transport and shipping of the CB unit between the CB Collection Site and the CB Processing Facility shall be designed to protect the integrity of the CB unit and the health and safety of personnel.*

**Explanation:**

CBBs should describe in their procedures how to protect CB unit integrity after collection.

**Evidence:**

The transportation and shipping process described by the facility should account for variables such as time, temperature, and type of container. This includes conditions during storage prior to shipping.

**STANDARD:**



C7.3 *The primary CB collection bag shall be placed in a sealed secondary plastic bag to contain any leakage from the primary bag.*

C7.4 *The CB unit shall be transported or shipped with required accompanying records as defined in Standard Operating Procedures.*

**Explanation:**

The records that should accompany the CB unit at transportation and/or shipment depend on the methods in place at the CBB and the CB Collection Site. Therefore, the Standards are not prescriptive, but require the CB Collection Site to determine the records that must be sent with the unit. At a minimum, the required accompanying information as listed in Appendix I must be with the unit or on the label itself.

**Example(s):**

The records required for a fixed CB Collection Site may be different than those for a collection kit model. The informed consent process also makes a difference; for example, if the process is a two-step process, much of the information is most likely already at the CBB.

**STANDARD:**

C7.5 *CB units shall be placed in an outer container that is qualified and validated to maintain a designated temperature range around the CB unit to protect cell viability during CB unit distribution.*

C7.5.1 *The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transportation or shipping.*

**Evidence:**

There should be robust validation of the transport/shipping container to cover all scenarios of environmental conditions. Information regarding the validation process can be found in the QM Plan and SOPs, and with documentation of the validation study itself.

**STANDARD:**

C7.6 *The temperature of a CB collection kit shall be monitored from the time it leaves the CBB until it is received by the CBB.*

C7.6.1 *Documentation of these parameters shall be provided to the CBB and maintained in the CB unit file.*

**Explanation:**

These Standards require both a validated shipping/transport container and continuous temperature monitoring to track from the time the supplies leave the bank until their return.

Temperature monitoring helps identify if the kit was potentially placed in an environment outside the acceptable storage temperature range for the reagents and supplies.

**Evidence:**

The CBB must provide the inspector with the validation study for the shipping/transport container and printouts of temperature monitoring.

**STANDARD:**

*C7.7 When a CB unit is shipped, the temperature inside the transport container shall be continuously monitored.*

**Explanation:**

Containers used to transport and ship CB units must be thermally-insulated and sturdy enough to sustain regular usage without damage to the CB units. They should be designed in a manner so as to maintain stable temperatures, with or without gel packs or other temperature stabilizing materials. All containers must be validated for temperature extremes appropriate for the geographical location(s) where the CB is collected and shipped. Validation must include temperatures during storage and transportation.

Temperature ranges must be specified, even where room temperature is the designated temperature. The Standards distinguish between transport and shipping based upon whether a CB unit is distributed via trained personnel (transport) or when it is distributed via unattended freight (shipping, such as via FedEx trucks or airplanes). It is not necessary to continuously monitor the temperature of a validated container that is transported by trained personnel who understand how to minimize exposure to extreme temperatures and can recognize when the temperature may have been compromised.

**STANDARD:**

*C7.8 The outer container shall be labeled with the information required in the Cord Blood Unit Labeling table in Appendix I.*

*C7.8.1 The outer container shall be secured.*

**Example(s):**

The outer container may be secured through a locking mechanism, an anti-tampering seal, or some other method that minimizes the risk of accidental or purposeful opening of the container.

**STANDARD:**

*C7.9 Transportation and Shipping Records.*

*C7.9.1 A list identifying each CB unit and its associated samples, maternal samples, and documents that are enclosed in a package shall be included.*

*C7.9.2 Transportation and shipping records shall permit the tracking of the CB unit from the CB Collection Site to its final destination.*

*C7.9.3 Transportation and shipping records shall include:*

*C7.9.3.1 The CB Collection Site responsible for transporting or shipping the CB unit.*

*C7.9.3.2 The date and time of transport or shipment.*

*C7.9.3.3 The identity of the courier.*

*C7.9.3.4 The date and time of receipt of the package.*

*C7.9.3.5 The condition of the package upon receipt.*

**Explanation:**

The list identifying items enclosed in a package should clearly state what the CB Processing Facility should have received. This includes:

- Name or identifier of collection site,
- Quantity of CB included in each container,
- How many containers were shipped, and
- Records that allow identifying each individual CB unit.

**Evidence:**

Before shipment, a form should be filled out at the site of origin. The form should clearly state the required elements in C7.9.3.

**Example(s):**

The following is an example of a form that could be used to document transport and shipping information:

Collection site ID: \_\_\_\_\_

Total containers shipped: \_\_\_\_\_

Container ID	Number of units	Unit ID
A	2	CBx-112233 CBx- 112234
B	1	CBX-00007

Packed by Carol\*

Date and Time of departure: 04/18/12 at 17:35

Courier name: Joe\* Date of arrival at processing facility :04/18/12

Received by: Jane\* at 19:30

Condition of the container: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\* (signatures and initials on file.)

## **PART D: CORD BLOOD PROCESSING STANDARDS**

### **STANDARD:**

#### **D1 CORD BLOOD PROCESSING FACILITY REQUIREMENTS**

*D1.1 The CB Processing Facility shall be licensed, registered, and/or accredited as required by the appropriate governmental authorities for the activities performed.*

#### **Explanation:**

CB Processing Facilities must be appropriately registered, licensed, and/or accredited as required by applicable laws and regulations. National laws and regulations may require registration, licensure, or accreditation with the government or may require accreditation from professional organizations for the activities performed within the facility. In some countries, the actual CB units may also require licensure.

#### **Evidence:**

The inspector should be provided with documentation or other evidence of the registration, licensure, and/or accreditation of the CB Processing Facility with all applicable regulatory or government agencies. Copies of the relevant registration, licensure, and/or accreditation documentation must be submitted in advance.

If such documentation is not provided prior to the inspection, the inspector may ask to see it on site. The CB Processing Facility Director should know who in the institution is responsible for the registration, and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory agency during the on-site inspection.

#### **Example(s):**

Examples of requirements include FDA registration within the U.S., TGA licensing within Australia, and similar agencies within Europe and elsewhere in the world.

If a CBB is in the U.S., it must be registered in accordance with 21 CFR part 1271. The timing of registration should be within 5 days after beginning operations (21 CFR part 1271.21). If a bank outside the U.S. exports CB units to the U.S., it must be registered with the FDA and also have a U.S. agent. More information regarding registration with the FDA can be found at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm>.

In the EU, the competent authorities in the Member States shall ensure that all tissue establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU Directive and/or other national regulations, where applicable.

In Australia, an appropriate license for the manufacture of HPC, Cord Blood issued by the TGA is required.

Note that each activity performed by the institution must be registered, regardless of who performs the activity. A CB Processing Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services related to the same regulations.

### **STANDARD:**

*D1.2 There shall be designated facilities of adequate space, design, and location that prevent improper labeling, mix-ups, contamination, or cross-contamination of CB units during the following activities:*

- D1.2.1 *Performance of processing activities and ancillary functions.*
  - D1.2.2 *Preparation of, and safe, sanitary, and orderly storage of, the supplies, reagents, and equipment needed for processing, testing, cryopreservation, storage, and release.*
  - D1.2.3 *Storage of CB units prior to release or distribution.*
  - D1.2.4 *Maintenance of records.*
- D1.3 *The CB Processing Facility shall be secure in order to prevent the entrance of unauthorized personnel and protect daily operations, equipment, and records.*

**Explanation:**

The CB Processing Facility must be secure to prevent unauthorized personnel from entering the facility. If the CB Processing Facility consists of shared space between CB unit processing personnel and, for example, research personnel, all aspects of the facility that affect CB units must be protected and be in compliance with these Standards.

The use of shared equipment must be in compliance with these Standards, whether or not the actual person using the equipment is processing CB units or not. This is because the maintenance and use of the equipment has a direct impact on the quality of CB units.

**Evidence:**

The inspector will look for technological security measures or a method of ensuring only people with permission enter the facility. In addition to securing the entrance of the CB Processing Facility, the daily operations, equipment, and records must also be protected.

**Example(s):**

The CBB may use technological methods to secure the facility, such as the use of electronic badge scanners, or manual methods such as a list of authorized personnel, the use of visitor registers, and/or a policy that non-processing personnel (such as repair technicians or delivery personnel) are accompanied by processing personnel while in the facility.

**STANDARD:**

- D1.3.1 *The CB Processing Facility shall have oversight of non-processing personnel visiting the CB Processing Facility to maintain compliance with these Standards.*

**Explanation:**

Persons who are not employed by the CBB may be present in or routinely enter the CB processing area. When repair technicians or delivery personnel enter the CB Processing Facility, the CB Processing Facility staff must oversee these individuals to confirm their activities are in compliance with the standards relevant to their activities in the facility.

**Example(s):**

Environmental conditions, equipment cleanliness, and the use of facility space are examples of ways that personnel not employed by the CBB can affect the safety of CB units.

**STANDARD:**

- D1.4 The CB Processing Facility shall provide adequate lighting, ventilation, access to hand decontamination, and air quality to ensure adequate conditions for proper operations in compliance with Applicable Law.*
- D1.5 The CB Processing Facility shall be maintained in a clean, sanitary, and orderly manner.*
- D1.5.1 There shall be documentation of facility cleaning and sanitation.*
- D1.6 Environmental conditions that affect the safety and potency of the CB unit shall be defined, controlled, monitored, and recorded to demonstrate ongoing compliance.*
- D1.6.1 There shall be inspection of environmental control systems.*

**Explanation:**

Environmental considerations may include temperature and humidity control, ventilation and air filtration, and disinfection of the room and equipment at appropriate times. Environmental monitors such as measures of air quality (e.g., particle counts and/or microbial colony counts) along with control of humidity and temperature may be used to minimize airborne contaminants. Requirements will differ based upon Applicable Law and clean room designation (though clean rooms are not required by these Standards).

CB Processing Facility cleaning and sanitation must be performed and recorded on a regular basis in order to prevent contamination and cross-contamination of CB units. The methods used must be specified by an SOP. While the bench-top, biological safety cabinet, and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces that may be cleaned by outside vendors, such as floors, walls, and ceilings, also fall under this standard. Responsibility should be assigned for who performs the sanitation procedures, the methods used, and the schedule.

As with all other Standards, this standard is a minimum requirement. Individual countries may have more stringent requirements. CBBs must follow all applicable laws and regulations, especially if they are more stringent than this standard.

**Evidence:**

Records of environmental conditions such as temperature and humidity and their review should be available for review by the inspector.

The CB Processing Facility shall have an SOP detailing methods for facility cleaning and the maintenance and inspection of environmental conditions. Documented evidence of facility cleaning, including that performed outside of normal processing operation such as cleaning performed by outside vendors, must be maintained and available for review by the inspector.

**Example(s):**

Environmental conditions to be monitored may include temperature; humidity; ventilation; and air pressure, filtration, and classification. The CB Processing Facility may have a continuous monitoring system that records environmental conditions such as room temperature and humidity that facilitates periodic review of recorded data. Records should be made of environmental monitoring, e.g., review of temperature and humidity and results of air and/or surface sampling.

The facility may have a checklist for outside vendors performing cleaning/sanitization tasks that is signed upon completion.

**STANDARD:**

*D1.7 Critical CB Processing Facility parameters that may affect cellular therapy product processing, storage, or distribution shall be defined, controlled, monitored, and recorded to demonstrate ongoing compliance.*

*D1.8 CB Processing Facility environmental conditions for temperature; humidity; ventilation; and air pressure, filtration and classification shall be defined and, if appropriate, monitored for cell processing.*

*D1.9 Personnel Safety Requirements.*

*D1.9.1 The CB Processing Facility shall have procedures that utilize universal precautions and are designed to minimize risks to the health and safety of employees, volunteers, and visitors, including at least:*

**Explanation:**

The purpose of D1.9 is to require appropriate protection in place for those entering or proximate to the CB Processing Facility. Facilities must define the risks, minimize those risks, and have procedures for how to respond to exposure to potential contaminants. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure. Safety, infection control, or biohazard waste disposal procedures that are unique to the CB Processing Facility should be covered in the CB Processing Facility SOP Manual.

The main intent of D1.9.1 is to protect CB units and personnel from being exposed to hazardous agents.

**STANDARD:**

*D1.9.1.1 Bloodborne pathogens.*

*D1.9.1.2 Chemical hygiene.*

*D1.9.1.3 Hand washing and/or decontamination.*

*D1.9.1.4 Fire safety.*

**Explanation:**

The CB Processing Facility should have defined plans for responding to each of the hazards listed, including fire within or adjacent to the processing and laboratory areas.

**Evidence:**

The inspector should see instructions for personnel actions in the case of exposure to hazardous agents or if a fire alarm sounds. Posted routes for exiting the facility may also be used.

**Example(s):**

There should be documented reports of 'drills' for practicing the instructions for fire safety.

**STANDARD:**

*D1.9.1.5 Radiation safety, if applicable.*

**Example(s):**

For example, if a CBB is near a blood bank or within a hospital-based institution, personnel may be exposed to radiation and, therefore, the CBB is responsible for establishing procedures for radiation safety.

**STANDARD:**

*D1.9.1.6 Latex allergy.*

*D1.9.1.7 Power failures.*

*D1.9.1.8 Liquid nitrogen.*

*D1.9.2 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.*

**Explanation:**

These standards apply to facilities involved in processing CB units. All persons who may come into contact with blood or body fluids must have appropriate personal protective equipment available to them. This includes those exposed to HPC products. The type of exposure that may be encountered will determine the appropriate suitable protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be provided. Gloves must be provided whenever potential infectious exposure exists and when sterile procedures are required to protect the product, patient, and/or staff.

**STANDARD:**

*D1.9.3 The CB Processing Facility shall have written policies and procedures for action in case of exposure to communicable disease agents or to chemical, biological, liquid nitrogen, or, if applicable, radiological hazards.*

*D1.9.4 Medical waste shall be decontaminated and disposed of in a manner to minimize hazard to facility personnel and the environment in accordance with Applicable Law.*

**Explanation:**

Any potentially biohazardous material shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste. Radioactive waste must be discarded using methods approved by appropriate governmental agencies. Also, CB Processing Facilities should post warning signs wherever radioactive materials are in use. Facility personnel responsible for these activities should be identified.

**Evidence:**

If processing is underway during the day of inspection, the inspector will observe personnel for use of protective clothing and other biosafety precautions. If no processing procedures are conducted that day, a mock procedure should be demonstrated. Employee files must document compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. How CB units are handled and discarded (e.g., incinerator, waste field, etc.) must match the written protocols. Compliance with federal, national, and state regulations should be addressed by the facility. The presence of unused equipment, excessive traffic from unauthorized personnel, and/or inappropriate storage of reagents and supplies may also contribute an unsafe environment and should be reviewed and where possible addressed.



The facility policies and SOPs, including housekeeping and waste disposal, must document compliance with good biosafety procedures, including adherence to universal precautions and to federal, national, state, or provincial regulations regarding safety.

**Example(s):**

Training records for CB Processing Facility personnel in safety, including universal precautions for handling blood and biological substances, should be created and available for inspection. Safety training may be undertaken/provided as an individual training module/session or be addressed as a component of task-specific training.

The training in “Standard” precautions per the Center for Disease Control for handling blood is a requirement of the OSHA in the U.S.

Contaminated materials may be discarded by autoclaving, ultra-high temperature incineration, decontamination with hypochlorite solution, and, in some locations, the use of a landfill.

The facility should have a safety manual. The manual may be an institution-wide document available by hard copy or via computer. The facility may keep a condensed or summarized hard copy of the institutional safety manual in the CB Processing Facility. In this case, there must be written documentation of how the safety manual is kept updated with institutional revisions. Alternatively, an SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice. The use of electronic training programs that cover safety and infection control is acceptable but there must be evidence that the staff has reviewed this information.

**STANDARD:**

*D2 CORD BLOOD PROCESSING FACILITY PERSONNEL REQUIREMENTS*

*D2.1 All CB Processing Facility personnel shall comply with these Standards.*

*D2.2 All CB Processing Facility personnel shall be trained and competent as required by B2.4.*

**Explanation:**

The purpose of this standard is to maintain the safety of the CB unit. All CB Processing Facility personnel must comply with these Standards, including personnel who do not process CB units but share workspace with individuals who do process units and facilities contracted to perform processing activities for the CBB.

Processing personnel must be appropriately trained and demonstrate competence in the tasks they are required to perform within the CB Processing Facility. This applies to CB Processing Facilities that are contracted to perform CB unit processing activities for the CBB. (For more information regarding written agreements to perform a function of CB banking, see B2.) For personnel who do not process CB units, the CB Processing Facility should have documentation of their competency for activities relevant to the quality of CB units (for example, the use of shared equipment).

Specific requirements for key CB Processing Facility personnel are in B1. In addition to specific requirements for the CB Processing Facility Director, Section B also requires adequate staff for all assigned operations.

**Evidence:**

The records of training for processing personnel (including competency-based assessment) should be available for review by the inspector.

**STANDARD:****D3 POLICIES AND STANDARD OPERATING PROCEDURES**

- D3.1 The CB Processing Facility shall establish and maintain policies and/or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B2. These documents shall include all elements required by these Standards, be consistent with the policies and Standard Operating Procedures of the CBB, and address at a minimum:*

**Explanation:**

The intent of this standard is that the performance of each step in the life of a CB unit is documented, from unit acquisition to final disposition.

The CB Processing Facility must comply with the requirements for SOP management specified in Section B of these Standards. It is possible that the CB Processing Facility Director may be different than the CBB Director, or that the CB Processing Facility is a contracted facility; however, the SOP scheme must still meet these Standards. This includes required elements of each individual SOP, ability of personnel to access the SOPs at all times, personnel compliance with SOPs, and review and approval of the CBB Director or designee. Review B2 and B3 for more details.

**Evidence:**

Inspectors are provided with the CB Processing Facility's key policies and SOPs prior to visiting the facility to allow observation of conformance of personnel performance with the defined policies and procedures.

**STANDARD:**

- D3.1.1 CB unit acceptance criteria, processing, cryopreservation, and storage.*
- D3.1.2 Labeling of the CB unit, reference samples, maternal samples, and associated documents.*
- D3.1.3 Storage and retrieval of reference samples and maternal samples for testing.*
- D3.1.4 Communicable disease testing, microbial cultures, HLA typing, hemoglobinopathy testing, and other testing. Acceptance criteria for test results shall be described.*
- D3.1.5 Criteria for release of CB units from quarantine, including nonconforming CB units.*
- D3.1.6 Criteria for qualification of CB units available for search and administration, including nonconforming CB units.*

**Explanation:**

The typical way CB units are currently qualified is based on pre-cryopreservation data regarding cell counts, viability, CFU, and CD34. Additional testing based upon both pre-cryopreservation and post-thaw data is the subject of current research and may be applicable in the future. CBBs may choose to use validated post-thaw data regarding CFU recovery and viability, but this is not specifically required in this edition of the Standards.

In addition to defining quality parameters, the CBB should describe its qualification review practice, including identifying personnel with expertise to understand the technical aspects of the processing procedure, critical review of the freezing curve, and a determination that the endpoints of processing have met established criteria.

**Evidence:**

CBBs should indicate that this review is performed prior to listing in a registry database (making the unit available for searching) and again before release of the CB unit for administration.

**STANDARD:**

- D3.1.7 Personnel training and continued competency for the procedures performed.*
- D3.1.8 Facility management of supplies, maintenance and monitoring of equipment, cleaning and sanitation procedures, disposal of medical and biohazardous waste, and emergency and safety procedures.*
- D3.1.9 A disaster plan to ensure continuous safe storage and transport and shipping, if applicable, of the CB units.*

**Explanation:**

How the CBB deals with the scope of possible events that constitute real threats to personnel and inventory must be described. The plan should identify internal disasters (such as loss of vacuum in a liquid nitrogen tank) and external disasters (such as loss of power in a building structure in severe weather or other natural event). Community or regional disasters would necessitate a more comprehensive strategy, one that a facility may not have all the details for but should at least have considered. The plan should also indicate that any event requiring transfer of inventory or exposure of CB units to temperatures outside the CBB's prescribed ranges must be documented.

**Example(s):**

Examples could include transferring inventory from a compromised storage vessel to an alternative tank within the facility or in a neighboring facility if such an agreement or facility exists.

**STANDARD:**

- D3.1.10 Disposal of a CB unit.*

**D4 CORD BLOOD PROCESSING**

**D4.1 Acceptance Criteria.**

- D4.1.1 Upon receipt of a CB unit package into the CB Processing Facility, the package shall be inspected for the following at a minimum:
  - D4.1.1.1 The receipt of the package within an acceptable amount of time as defined by the CBB.*
  - D4.1.1.2 The integrity of the outer container and the temperature against validated parameters.*
  - D4.1.1.3 Verification of the contents of the package against the list of enclosed items.**

- D4.1.1.4 The integrity of the primary and secondary containers.*
- D4.1.1.5 The CB unit for appropriate appearance, integrity, labeling, and identification.*
- D4.1.1.6 The associated samples, maternal samples, and documents for appropriate labeling and identification.*
- D4.1.2 For unrelated CB units, an appropriately signed consent authorizing collection, processing, testing, and storage of the CB unit, associated samples, reference samples, and maternal samples for the intended purpose shall be present before processing is initiated.*
- D4.1.3 For related CB units, there shall be a signed agreement for collection, processing, testing, storage, and a name and contact information of the donor family.*
- D4.1.4 If a CB unit collected for related use may subsequently be released for unrelated use, there shall be informed consent for such release obtained before processing.*

**Explanation:**

For related CB units, the signed agreement must include the name of the intended recipient if applicable. This may not be applicable to some CB units that are stored at the request of a donor family to be used in the future for purposes not known at the time of the agreement. An informed consent is generally signed for testing the maternal blood for infectious disease markers as surrogate testing for the CB unit.

**Evidence:**

The inspector should observe the process by which CB units are received into the CB Processing Facility to determine if staff members are following appropriate SOP and policies.

**Example(s):**

Examples of what should be included in the transfer box include the following:

- The packing list, referencing all CB units in that shipment,
- Related associated samples,
- Consents, and
- Related documentation.

**STANDARD:**

*D4.2 Processing.*

- D4.2.1 Only properly labeled and clearly identified cord blood units shall be accepted for processing.*
- D4.2.2 CB units during all stages of processing shall minimally contain an affixed in-process label with the CB unit unique identifier at a minimum.*
- D4.2.3 Information regarding processing steps that have been completed on a CB unit shall accompany the CB unit or be available electronically during all stages of processing.*

*D4.2.4 Processing and cryopreservation of CB units shall be performed according to Standard Operating Procedures validated to result in acceptable viability and recovery.*

**Explanation:**

Validation studies should include the tests required by these Standards in D10. The rationale for chosen end-points should be documented (for example, in a validation study, retrospective analysis, trending, etc.).

The CB Processing Facility Director should determine what and how processing methods will be validated. Validation may be retrospective, concurrent, or prospective. Validation should include retrospective and/or ongoing evaluation of processing results, data analysis, establishment of expected ranges and means and/or medians, and periodic documentation that the procedure is yielding results within the expected range. This analysis may be best performed at the time of SOP review.

New procedures introduced into the CB Processing Facility should undergo prospective validation when possible. Prospective validation of a processing procedure may be accomplished by performing a mock procedure using a surrogate CB unit. When no surrogate units are available for a full-scale procedure, validation using a small portion of a unit and a scaled-down procedure may be adequate. Ultimately, validation of the quality of the unit is determined by timely engraftment of the transplanted cells and the clinical outcome of the recipient. When CB is used for regenerative medicine or for transplant for other than hematopoietic and immune diseases, post behavioral tests may be considered as a measure of unit quality along with viability of thawed CB pre-infusion. However, for all CB units, there should be *in vitro* studies demonstrating that the desired end-point of the processing procedure was achieved.

In some cases, the CB Processing Facility may implement a processing procedure or process that has been validated by another facility and/or has been published. In such cases it may not be necessary to undergo a full validation study; rather the facility may need only to verify that the procedure or process results in comparable CB units when performed locally. It remains important that a formal process be followed and that objective acceptance criteria are established.

**Evidence:**

The inspector must review one or more validation or verification studies to determine if the requirements of these Standards are met.

End-points and specifications may be based on in-process results or on final CB units.

**STANDARD:**

*D4.2.4.1 Critical control points and associated assays shall be identified and performed on each CB unit as defined in Standard Operating Procedures.*

**Explanation:**

The CBB must define certain points in the processing and cryopreservation periods where personnel should double check that processes are being performed correctly and are achieving the desired result.

**Example(s):**

A CBB may document that critical control points are checked by using a checkbox on a worksheet or indicating the initials of one or more personnel who double checked the point.

**STANDARD:**

*D4.2.4.2 Failure of the processing procedure to achieve acceptable end-points or specifications shall be evaluated and documented.*

**Explanation:**

For unrelated CB units, where Applicable Law requires minimal processing/cryopreservation endpoints (e.g., U.S. licensed CB units), these endpoints will determine unit acceptance.

**Example(s):**

Examples of end-points include the following:

- A minimum threshold for nucleated cell yield after processing (for example, percent recovery or total count),
- Post-processing viability,
- Potency/CFU assays,
- CD34 cell content,
- Target limit for final volume after processing, and/or
- Maximum time between collection and freezing, between start of processing and cryopreservation, and/or between finishing volume and cryopreservation.

**STANDARD:**

*D4.2.5 Methods for processing shall employ aseptic technique and CB units shall be processed in a manner that minimizes the risk of mix-ups and cross-contamination.*

*D4.2.5.1 Where processing of CB units involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.*

*D4.2.5.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.*

**Explanation:**

The simultaneous presence of CB units from more than one donor in a CB Processing Facility is a frequent occurrence. Procedures must be in place to prevent the possibility of mix-ups or cross-contamination of units in such circumstances. Procedures should define safeguards to be employed, such as forbidding units from more than one donor to be in the Biological Safety Cabinet at any one time and should describe the cleaning and disinfection practices to be used for sequential processing using the same equipment.

Whenever possible, closed systems should be used for all processing steps. This is important not only to reduce the likelihood of microbial contamination during processing, but of cross-contamination with other infectious agents or even with cells from other CB units. GTP regulations specifically forbid the pooling of products from more than one donor during processing so as to reduce the risk of communicable disease transmission. Recently the use of CB from two or more donors for a single transplant procedure has been used. In such cases, it is acceptable to sequentially thaw and infuse products from different donors, but it is not acceptable to pool the products into a single container for infusion. For some CB units processed under approval by regulatory agencies as specified in INDs, IDEs, or an equivalent approval pathway, pooled cells may be part of the manufacturing process. However, this step would have been reviewed by the competent authority and would thus be allowed by these Standards.

**Evidence:**

The inspector should observe the CB Processing Facility in operation and should ask personnel what processes are in place when multiple CB units are received into the facility on the same day. The inspector should determine (from direct observation and/or by reviewing SOPs) that aseptic technique is utilized during processing.

**Example(s):**

Other methods to prevent mix-ups may include identification of reagents as dedicated to a single processing procedure and a separation of records to avoid a mix-up of information.

**STANDARD:**

- D4.2.6 *Cryopreservation of unrelated CB units shall be initiated within 48 hours of collection.*
- D4.2.7 *Cryopreservation of related CB units shall be initiated within 72 hours of CB collection.*

**Explanation:**

These Standards are purposefully conservative for unrelated CB units with the goal of building a quality inventory and preparing a CB unit in the shortest time possible to retain the immature characteristics of the cells contained within the unit. Studies have demonstrated that cells remain functional up to 72 hours past collection (Transfusion, Vol. 45 Issue 6 Page 842 June 2005, *Results of the Cord Blood Transplantation (COBLT) Study unrelated donor banking program*, Joanne Kurtzberg, Mitchell S. Cairo, John K. Fraser, LeeAnn Baxter-Lowe, Geoff Cohen, Shelly L. Carter, Nancy A. Kernan), yet others have claimed that important loss of mononuclear cells occurs after 24 hours and CB held for 72 hours showed higher levels of cell deterioration (Transfusion Volume 43 Issue 5 Page 626 - May 2003, *Short-term liquid storage of umbilical CB*, Allison Hubel, Dale Carlquist, Mary Clay, and Jeffrey McCullough. J Hematother Stem Cell Res. 2003 Feb;12(1):115-22. *Assessment of cell viability and apoptosis in human umbilical CB following storage*. Xiao M, Dooley DC).

Due to the nature of related CB units, which donor families collect for purposes of related or autologous use, cryopreservation must be initiated within 72 hours of CB collection.

**Evidence:**

The inspector should review processing/cryopreservation records to determine that policies and SOP are in place and are adhered to confirm that cryopreservation is initiated within the defined time period. This should be evident in the CB unit's processing documentation.

**Example(s):**

The delay of a related CB unit from a family with a history of leukemia due a snowstorm is an example of a single deviation that may be accepted by the CBB and documented in accordance with its QM Plan.

**STANDARD:**

- D4.2.8 *More than minimal manipulation of a CB unit shall be performed in accordance with Applicable Law and:*
  - D4.2.8.1 *Using reagents and/or devices approved for that manipulation by the appropriate governmental agency or*

*D4.2.8.2 With an Institutional Review Board or Ethics Committee-approved protocol or*

*D4.2.8.3 With an Investigational New Drug Protocol, Investigational Device Exemption, or non-U.S. equivalent.*

**Explanation:**

Volume reduction of the collected CB unit by depletion of red blood cells and plasma decreases the incidence of infusion-related hemolysis and/or DMSO toxicity while allowing more efficient long-term storage. Some studies assessing contaminating red cells in marrow suggest that red blood cells may affect the functionality of the cells<sup>1</sup> and another study suggests it may have an inhibitory effect on T-cell proliferation<sup>2</sup>. Though some CBBs are concerned that any attempt at cell manipulation and concentration might result in a considerable cell loss and possibly impair engraftment, the majority of CBBs have adopted this practice. Simple plasma depletion is still performed in some CBBs for this reason, but in accordance with this standard, this practice must be approved by appropriate validation and oversight.

If reagents and/or devices are used, a written approval letter expressing acceptance from the Clinical Program should be obtained prior to releasing the CB unit.

**Reference:**

1. Assmus B, Tonn T, Seeger FH, Yoon CH, Leistner D, Klotsche J, Schächinger V, Seifried E, Zeiher AM, Dimmeler S. Red blood cell contamination of the final cell product impairs the efficacy of autologous bone marrow mononuclear cell therapy. *J Am Coll Cardiol.* 2010 Mar 30;55(13):1385-94.
2. Bernard A, Meier C, Ward M, Browning T, Montgomery A, Kasten M, Snow C, Manning E, Woodward J. Packed red blood cells suppress T-cell proliferation through a process involving cell-cell contact. *J Trauma.* 2010 Aug;69(2):320-9.

**Evidence:**

If possible, the inspector should observe the processing of CB units and verify that processing personnel are adhering to the validated or verified policies and procedures set forth in the SOP.

**STANDARD:**

*D4.2.9 Equipment, supplies, and reagents shall not adversely affect the viability of the CB units and shall not permit the introduction of adventitious agents or the transmission or spread of communicable disease.*

**Explanation:**

Criteria for the selection and approval of equipment and materials used for CB unit processing must include the elements in D4.2.9 and the processing process must be validated to confirm the same.

**Evidence:**

Equipment qualification records, materials management procedures, and process validation studies must all include consideration of the potential effect on the viability and sterility of the processed CB unit.

**STANDARD:**

*D4.3 At the completion of processing prior to cryopreservation, the freezing bag shall be labeled with the information as required by the Cord Blood Unit Labeling table in Appendix I.*



*D4.4 Records pertinent to the CB unit shall be reviewed by the CB Processing Facility Director or designee and found to be acceptable prior to the release from quarantine status.*

**Example(s):**

Records include medical information for which review could be delegated to the CBB Medical Director.

**STANDARD:**

*D5 REFERENCE SAMPLES AND MATERNAL SAMPLES*

*D5.1 At a minimum, the following reference samples shall be collected from the CB unit prior to cryopreservation:*

**Explanation:**

These requirements for reference samples apply to all CB units (unrelated and related) unless otherwise specified.

**Evidence:**

The inspector needs to look for SOPs or policies describing how many and what type of samples the CBB routinely obtains.

**STANDARD:**

*D5.1.1 A minimum total volume of at least 200  $\mu$ L divided into at least two segments with each sealed and integrally attached to each freezing bag.*

**Explanation:**

These reference samples are stored as segments because the tubing from which they are made shares the same fluid path as the CB unit, and are therefore certain to be identical to the CB unit. These Standards are open to flexibility in allowing innovation in this area, as long as the material is confined within tubes or containers that are integrally attached to the CB unit. If a unit is stored in two bags, then each bag must have two segments.

The concept behind the use of this material is that it best represents the cryopreserved CB unit considered for use in administration. The material within the segments has undergone the identical collection, processing, cryopreservation, and storage conditions as the CB unit. Therefore, it is possible to infer the identity, viability, and perhaps the potency of the CB unit within the cryobag from testing performed on these segments.

The volume required in this standard is based upon the theory that this volume will be adequate starting material for the tests to be performed; however, this is dependent on the concentration of cells within the CB unit after collection and processing. The CBB must validate that the concentration of cells after using its collection and processing methods is sufficient for confirmatory typing and other tests that need to be performed on these samples. If it is not, the CBB may need to store a higher volume.

The relationship between testing from segments and the results obtained from the CB unit should be studied.

**Evidence:**

The inspector needs to ask for a validation of the testing performed in those samples to prove that the amount collected and stored is representative of the final product and any testing performed out of those samples is accurate and reliable.

**Example(s):**

An example of the validation could be measuring the volume of each of the segments and performing a test for HLA type, CD34, viability, etc. out of those segments from a CB unit used with the purpose of validation.

**STANDARD:**

*D5.1.1.1 The contents of each reference sample shall be representative of the CB unit.*

**Explanation:**

It is imperative that the CB Processing Facility protects the integrity of the sample contained in these segments.

The individual doing the filling must mix the CB unit well and fill both bag and segments simultaneously so that segments truly represent the contents of the bag.

**Evidence:**

The inspector could confirm that the leak test is included in a validation to make sure that the instrument or methodology used to make the seals work properly.

**STANDARD:**

*D5.1.1.2 When a CB unit is initially requested, a minimum of one (1) segment shall be used to confirm the results of HLA typing and should be used for cell viability and/or potency analysis.*

**Explanation:**

Caution must be used when separating segments from the CB unit as welds may break in a manner that exposes blood to the storage environment. If that environment is liquid nitrogen, the entire inventory contained within that vessel may be at risk to undetected agents in the exposed CB unit.

Verification typing need not be performed with every request for a CB unit. HLA must be confirmed one time from an integral segment and the results made available in the information relayed to each Clinical Program interested in that CB unit.

The use of an integrally attached segment for cell viability and/or potency analysis is recommended, though it is understood that segments may not be available for this testing if they have already been used for verification typing, cell counts are too low, etc. A reference sample stored in a cryovial would be acceptable if a segment is not available.

Articles have been published to describe methods of determining identity (HLA) and evaluating potency or viability on the same segment, reserving remaining segments for future requirements or the Clinical Program. But these tests can be performed on distinct segments on separate occasions, depending on the rationale for testing and/or policy of a CBB.

**Evidence:**

CBB policies and demonstrations should provide evidence of vigilance when separating segments from the CB unit.

**Example(s):**

Potency and/or viability analysis can be performed as directed by the CBB's policies, either for internal quality evaluations or at the time of initial or subsequent CB unit requests for as long as segments remain.

**STANDARD:**

*D5.1.2 Additional samples of a minimum total of  $2 \times 10^6$  nucleated cells divided into at least two (2) vials or additional contiguous segments.*

*D5.1.2.1 Reference samples intended for viability or potency analysis shall be stored at the same temperature as the CB unit.*

**Explanation:**

These samples are in addition to the integral segments required for CB unit identity and viability. Viable cell aliquots must be retained to permit testing of a CB unit's biological features, such as enzymatic activity when the CB unit will be used for transplantation in metabolic diseases. However, since these samples are likely to be handled, cryopreserved, and stored differently from the actual CB unit, they will not be useful for product identity or indicative of product viability or potency.

**Evidence:**

The inspector needs to ask for a validation of the testing performed in those samples to prove that the amount collected and stored is representative of the final product and any testing performed out of those samples is accurate and reliable.

**STANDARD:**

*D5.1.2.2 Reference samples used for purposes other than viability or potency analysis shall be stored at  $-70^{\circ}\text{C}$  or colder.*

**Explanation:**

The requirement for storage of reference samples at  $-70^{\circ}\text{C}$  or colder is intentionally conservative to provide the best samples for unanticipated tests in the future. Some infectious diseases already require storage at this temperature.

**STANDARD:**

*D5.1.3 A minimum total volume of 3.6 mL of serum or plasma from non-heparinized samples divided into at least two vials.*

*D5.1.3.1 The serum or plasma should be stored at  $-70^{\circ}\text{C}$  or colder.*

*D5.1.4 Suitable material for preparation of at least 50  $\mu\text{g}$  genomic DNA.*

*D5.2 A retention sample from the CB unit should be stored indefinitely.*

**Explanation:**

Retention samples are useful for investigating adverse events or retroactive quality control activities. Indefinite storage does not mean that the sample must be stored forever; it means that no time limit for storage can be established. It is understood that once a retention sample is used for the purposes stated above that the sample will no longer be available.

The rationale for volume requirements in a multiple of 1.8 mL is because standard vials are of this size.

**Example(s):**

In the U.S., the FDA requires storage of retention samples from unrelated CB units.

**STANDARD:**

*D5.3 Maternal samples to be maintained shall include:*

*D5.3.1 From the birth mother, a minimum total volume of 3.6 mL of serum and/or plasma from non-heparinized samples divided into at least two vials.*

*D5.3.1.1 The serum or plasma shall be stored at -70°C or colder.*

*D5.3.2 From the genetic mother, suitable material for preparation of at least 50 µg of genomic DNA with the exception of egg or embryo donors.*

**Example(s):**

Material suitable for preparation of genomic DNA may be purified DNA, frozen cellular material, or blots.

**STANDARD:**

*D6 CRYOPRESERVATION*

*D6.1 CB units shall be cryopreserved using controlled rate freezing or an equivalent procedure validated to demonstrate recovery of viable and potent cells.*

**Explanation:**

Validation should demonstrate a temperature cooling rate with acceptable endpoint temperatures and include viability or potency tests required in D10.

Validation studies should include the duration of cell exposure to the cryoprotectant prior to the initiation of the cryopreservation program while demonstrating cell viability/potency to length of DMSO exposure. One can then determine how many CB units can be simultaneously processed within a timeframe that maintains acceptable cell viability. For CBBs that freeze multiple units at a time, studies should demonstrate consistency of DMSO addition and cryopreservation between various numbers of CB units so that processing staff know the limitations of their system.

**Evidence:**

The inspector should review CB cryopreservation temperature graphs that demonstrate starting and endpoint temperatures. CB unit graphs should correspond to validated temperature graphs that have been approved by the CBB.

A CBB's policies should emphasize attempts to minimize the time between addition of DMSO and initiating cryopreservation. This can also be included as a key element in staff training and evaluated at the time of competency assessment.

**Example(s):**

Although controlled rate freezing by use of a programmable device is the recommended method for cryopreserving CB units, alternative methods validated to protect cell viability may be used. Other methods of freezing (e.g., freezing in a mechanical freezer) can be acceptable with the appropriate level of vigilance:

- Ensure that canisters are separated, not stacked, to allow airflow around each unit.
- Limit access to the freezer during the freezing process so the temperature within the interior is not compromised.
- Trace the freezing kinetics via a data logger or other alternative tracing device to produce a cooling curve that demonstrates acceptable execution.
- Use methods demonstrated to result in acceptable post thaw viability and potency.

One acceptable viability method is the use of a Flow Cytometer and a fluorescent dye.

**STANDARD:**

*D6.2 Cryopreservation Standard Operating Procedures shall specify that the following information is recorded for each unit:*

*D6.2.1 Total nucleated cell concentration within a defined range.*

*D6.2.2 The cryoprotectant, its final concentration, and the duration of cell exposure prior to freezing.*

*D6.2.3 Method of freezing and end-point temperature of cooling.*

*D6.2.4 Cooling rate within a defined range and continuous monitoring of the temperature.*

*D6.2.5 Freezing curve parameters within a defined range.*

*D6.2.6 Storage temperature.*

**Explanation:**

The storage temperature should be specified as a defined range rather than a precise single temperature, which is unnecessary and difficult to maintain.

**Evidence:**

The inspector should review the SOP for acceptable cryopreservation parameters. The SOP should be detailed in the descriptions of the cryoprotectant used and the final concentration of both TNC and cryoprotectant.

**STANDARD:**

*D6.3 CB units shall be stored in freezing bags designed and approved for the cryopreservation of human cells and shall be placed into metal canisters to provide protection during freezing, storage, transportation, and shipping.*

**Explanation:**

The use of vials to provide long-term storage is not acceptable at this time. While it is possible that future innovation may modify this standard, the use of vials has a possibility to increase contamination, and may be difficult to prepare for infusion in the Clinical Program. CB units stored in vials prior to these Standards can still be used; however, the CBB should inform the Clinical Program so that the appropriate planning for storage and infusion can take place.

**STANDARD:**

- D6.3.1 Each freezing bag and its satellite container(s), if any, shall be examined visually for damage or possible contamination prior to use.*
- D6.3.2 Reference and retention samples to be used for viability, potency, or stability study assays shall be cryopreserved and stored in the same manner as the CB unit.*

**Explanation:**

Segments must be appropriately identified to allow accurate tracing to the CB unit in the event the segment becomes detached from the unit (for example, if they become detached during the cryopreservation procedure). The segment should be identified in a manner that allows traceability of all steps performed on the CB unit and donor.

**Evidence:**

The inspector should visually observe the filling and labeling process of the cryobag prior to cryopreservation. At a minimum, the SOP should clearly define this process.

**Example(s):**

One way to comply with this standard is through the use of labels or stickers; however, the CBB may decide how to identify the sample as long as it accurately traces it to the CB unit.

**STANDARD:**

*D6.4 Processes must minimize the risk of overfilling and underfilling freezing bags.*

- D6.4.1 After filling, each freezing bag shall be visually examined for possible leaking, overfilling or underfilling of the freezing bag, and breakage of seals. The results of these inspections shall be documented.*

**Explanation:**

Overfilling is defined as exceeding the manufacturer's volume recommendations. Underfilling can be equally detrimental to product safety as bags would be thinner, more brittle, and particularly susceptible to breakage. Exposure of product to nitrogen, whether liquid or vapor phase, is in itself a hazard because liquid nitrogen is not sterile. Aerosols are created in the vapor phase above the liquid when materials warmer than -196°C are introduced into the liquid. These issues have resulted in broken seals and bags that explode as the bag rapidly expands when exposed to warmer temperatures, even that of nitrogen vapor.

For CBBs that use overwraps, removal of excess air in the overwrap bag is extremely crucial. Temperature shifts can cause ballooning of the overwrap and eventually explosion and breakage of the overwrap.

**Evidence:**

The CB Processing Facility's policies should include guidelines to remove air and prevent overfilling or underfilling of the freezing bags.

**STANDARD**

**D7 CONDITIONS FOR STORAGE**

- D7.1 Each CB unit storage device shall be located in a secure area. The device and/or the area shall have locking capability that is used at least when the area is not occupied by the CBB staff.*

**Explanation:**

A secure environment is one where the general public or unauthorized persons do not have access, i.e., where opportunity for tampering with the CB units and their accessory components is reasonably minimized.

**Evidence:**

A secured access requires a method to allow authorized staff to enter and to prohibit access by unauthorized staff.

**Example(s):**

A physically secured area such as: (1) key card access to laboratory or a specific storage area or room for staff authorized to have access to CB unit storage; (2) a physically locked area where authorized staff have keys, or (3) for settings where access is not limited when CBB staff are present, a method to provide security when staff are away from the work area such as “off-hours” or at meetings “off-site” is required.

**STANDARD:**

*D7.2 Refrigerators and freezers used for the storage of CB units, blood components, human cells, tissues, specimens, or reagents used in CB unit collection, processing, or cryopreservation shall not be used for any other purpose.*

*D7.3 Procedures to minimize the risk of microbial cross-contamination of CB units shall be defined and maintained.*

**Explanation:**

CB units, samples, and reagents should be stored in storage settings appropriate for the contents to maintain their integrity and potency and in an organized manner, with segregation, as appropriate. Storage controls should minimize risk of contamination between units that are in-process, units with identified risk, and those available for release. The process should be validated to be effective.

**Evidence:**

Records of CB unit storage demonstrate use of quarantine as defined in storage SOPs in use at the CBB.

**Example(s):**

There are several approaches that the CBB may choose from to minimize the risk of cross-contamination. In addition to quarantine of all CB units until the CBB Director or designee has approved the release of the CB unit, the CBB may overwrap the CB unit with a second plastic bag or store at-risk units in vapor phase liquid nitrogen storage.

**STANDARD:**

*D7.4 Processes for storing CB units in quarantine shall be defined in Standard Operating Procedures.*

*D7.4.1 Quarantined CB units shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.*

*D7.4.2 Each CB unit shall be maintained in quarantine storage until the CBB Director or designee has approved the release of the CB unit from quarantine status based upon review of maternal communicable disease risk history, other medical history, maternal test results, and CB unit microbial culture results as required by Applicable Law.*

**Explanation:**

Because results of all testing and screening of mothers and CB units are not completed prior to collection, quarantine is required until results are available and the CBB Director or designee has approved the release of the CB unit from quarantine. This can occur after the completion of testing, confirmation of acceptable test results, and a review of maternal risk factors and family medical history. In settings where a unit with an identified infectious disease risk is not discarded, the unit must be stored in a manner to physically separate the unit from other inventory and should include segregation or designation in an automated electronic system.

Related, unrelated and autologous CB units may be placed in long-term storage together, provided a robust inventory management system is used that provides (1) appropriate segregation of inventory and methods to minimize cross-contamination and (2) systems to support identity and location of the CB unit. Inventory controls should support prevention of mix-ups and pre-mature release.

**Evidence:**

Each CBB must have an SOP to define storage areas and include processes and controls for quarantine and release, as well as segregation, as applicable to the facility setting. Each record must be reviewed to confirm specified release criteria have been met prior to transfer or assignment of permanent status. In-process units and units with infectious disease risk or units not acceptable for clinical use must be stored in a manner that distinguishes them from those acceptable for release in compliance with Applicable Law.

**Example(s):**

SOPs define the quarantine and release process and accommodate methods to maintain units with known infectious disease risk in a manner to prevent cross-contamination. Quarantine may be temporal, physical, or a designation within the CB unit record. Some CBBs, particularly those using automated equipment and/or overwrap, store the CB unit in a permanent location directly after cryopreservation. In these cases, “release” may refer to the process of making a CB unit available for listing and distribution by assigning a permanent disposition status rather than physically relocating the CB unit. Records of unit storage clearly delineate storage locations for units as they move from quarantine and in-process locations to release to long-term storage locations, as defined in facility procedures.

Quarantined storage can be achieved in a variety of ways:

- Storage in nitrogen vapor freezers eliminates contact through liquid nitrogen.
- Proper overwrap of CB units avoids contact even in liquid and can be an acceptable manner to quarantine units, including those positive for bacterial contamination. However, procedures must be in place for when the overwrap is violated. When segment removal violates the overwrap and:
  - the CB unit has no evidence of infectious disease risk through testing or screening, it is appropriate to store the CB unit with other units with no increased infectious disease risk.
  - or
  - the CB unit has identified infectious disease risk through donor testing or screening is positive for infectious disease excluding CMV and deemed acceptable for retention by the CBB Medical Director, it must be placed in appropriate quarantine method where it poses no contamination risk to other CB units.



**STANDARD:**

*D7.4.3 Records shall indicate when a CB unit was released from quarantine into permanent storage.*

**Explanation:**

Some CB units, such as those that are overwrapped, may already be physically located in their permanent storage assignment. Documentation of release must be available whether the CB unit is physically transferred or simply assigned a new disposition.

**Evidence:**

CBBs that quarantine CB units in vapor phase and subsequently transfer them into liquid nitrogen storage upon approval by the CBB Director or designee must document this activity in the CB unit record.

**Example(s):**

Records of unit storage clearly delineate storage locations and/or designation for units as they move from quarantine and in-process locations to release to long-term storage locations, as defined in facility procedures.

**STANDARD:**

*D7.4.4 CB units shall remain quarantined if the reference samples or maternal samples have reactive and/or positive screening test results for communicable disease or increased infectious disease risk obtained through the donor screening process.*

**Explanation:**

When tests identify increased infectious disease risk, these units must be managed in a manner to limit risk of cross-contamination using methods to physically separate the CB unit from other units as noted above. Per FDA, a donor whose specimen is reactive on a screening test for a communicable disease agent is considered at increased risk of infectious disease, regardless of the results of more specific or confirmation assays (except for a donor whose specimen tests reactive on a non-treponemal screening test and negative on a specific confirmatory assay and CMV testing). Increased infectious disease risk may also be identified through the donor medical history, physical exam, review of delivery records or other medical records, as well as unit testing, as required by national competent authorities.

**Evidence:**

The CBB shall have an SOP defining storage controls used to separate and segregate units with increased risk of infectious disease through donor screening and testing or CB unit testing, including electronic designations, as applicable.

Review of records for units with increased infectious disease risk and those without such risk should show the appropriate storage locations and designations as defined in the facility SOP(s).

**Example(s):**

Examples of physical separation to limit risk of cross-contamination include the use of an overwrap or storage in vapor phase. Such CB units should be segregated from units without identified risk using separate storage device or designation in an electronic system.

**STANDARD:**

*D7.5 Temperature.*

*D7.5.1 CB units shall be stored at -150°C or colder.*

*D7.5.1.1 If CB units are not fully immersed in liquid nitrogen, the storage freezers shall be qualified to show that all CB units are maintained at appropriate temperatures.*

*D7.5.1.2 Transfer of cryopreserved CB units shall be validated and monitored.*

**Explanation:**

The absolute temperature of liquid nitrogen is -196°C; therefore, it is accepted that CB units stored in liquid nitrogen will be at this temperature. However, digital monitoring displays may not read this exactly but within a range around this temperature. The CB Processing Facility must establish a range of acceptable temperature readings.

If CB units are not fully immersed in liquid nitrogen, the storage system must be validated to prevent CB unit storage above -150°C and include a continuous temperature monitoring system that records temperatures at least every 4 hours. For storage systems where units are fully immersed in liquid nitrogen, the storage system must provide levels adequate to maintain specified temperatures. At no time should the facility's mechanism for long-term CB unit storage support storage at temperatures warmer than -150°C. Electronic monitoring systems for either temperature or liquid nitrogen levels should include alarm mechanisms that are tested periodically.

This requirement is based on evidence that long-term storage at warmer temperatures decreases potency. In addition, the warmer temperature of -135°C is closer to glass transition phase and provides less opportunity for CBBs to address facility or storage issues that could compromise CB unit integrity. The evolution in construction of vapor storage vessels is such that stability of the temperature within all sections of the storage area is more consistent than older vapor storage freezers. With this new design, more CBBs are choosing to store in vapor because this method achieves similar performance as liquid nitrogen storage without liquid nitrogen contact, further eliminating some of the risks of cross-contamination.

**Example(s):**

Records of continuous temperature monitoring devices are available for review and include recording of temperatures every 4 hours at a minimum. Records for monitoring systems for liquid nitrogen levels demonstrate adequate levels, as defined by CB Processing Facility. Electronic alarm systems should include records of alarm testing.

**STANDARD:**

*D7.5.2 Warming events at any time after the process of storage and/or distribution shall be minimized.*

*D7.5.2.1 The duration of warming events shall be documented, and the impact on the CB unit shall be assessed.*

*D7.5.2.2 If a warming event may have potentially decreased the potency of an unrelated CB unit, the unit shall not be made available for distribution for administration.*

**Explanation:**

CB units must be maintained at the specified storage and transport temperatures. The CBB must have validated procedures to remove CB units and/or samples in a manner that protects cell viability. Deviations from these procedures must be documented in accordance with the QM Program.

According to industry publications, the potential for significant warming events can occur when the CB unit temperature rises above  $-132^{\circ}\text{C}$  (the glass transition phase, which is a non-equilibrium, disordered solid state that achieves real time structural stability). Because CB unit volumes are small and are frozen in bags with large surface areas, their thermal kinetics are greatly affected by their environment. After cryopreservation, CB unit temperatures that transverse the glass phase will adversely impact the integrity of the cells. The CB Processing Facility must determine how its processes influence CB unit temperatures so it can be aware of the instances when glass phase is approached. For instance, validation may include mimicking the activity of retrieving a CB unit to secure a segment for confirmatory testing. Temperatures of CB units at the top and the bottom of the rack and time of exposures outside of liquid nitrogen would be tracked to determine the length of time it takes for each to approach  $-150^{\circ}\text{C}$  and  $-120^{\circ}\text{C}$ . This validation includes temperature extremes such as exposure of a CB unit to ambient air and how long it takes to reach  $-132^{\circ}\text{C}$ , and how temperatures are affected by vapor phase storage.

CB unit inventory must be managed in a way that minimizes variations in temperature. Opportunities for significant warming events occur when a CB unit is outside of its proper storage temperature for extended periods of time. Examples of these opportunities include:

- Transfer of CB units from a controlled rate freezing device to quarantine storage vessels,
- Transfer of CB units from quarantine to long-term storage,
- Removal of segments for confirmatory testing,
- Removal of a rack so that a segment can be removed from a CB unit that occupies the same rack, and
- Storage of CB units in older vapor vessels that exhibit unstable temperatures when open.

**Evidence:**

Significant warming events do not necessarily occur every time the lid is opened, but these concepts must be addressed in CBB policies and are avoided by staff during execution of activities that prolong exposure of CB units to temperatures warmer than  $-150^{\circ}\text{C}$ . Temperature excursions should be avoided, but if they occur, a process to address the impact to affected units is required. Temperature excursions should be included as an aspect of stability programs, as described above.

At the end of processing and all accumulated transfers, a CBB should be able to demonstrate that the process results in a viable CB unit.

**Example(s):**

Standard Operating Procedures define processes to limit unnecessary exposure to temperatures below  $-150^{\circ}\text{C}$ , including routine processes for CB unit transfer and segment removal. Validation testing records include facility-specific data to support acceptable unit viability for temperature excursions related to significant warming events. Procedures and records support the documentation of duration of warming events and the impact to the affected CB units.

To avoid opportunities for exposure of CB units to temperatures outside proper ranges, a CBB might recommend that transfer of CB units be done in liquid nitrogen vapor, though this is not a standard nor is it necessary in all cases.

**STANDARD:**

D8 MONITORING AND ALARM SYSTEMS

- D8.1 Refrigerators used for storage of CB units before cryopreservation of the CB unit shall have a validated system to monitor the temperature continuously or record the temperature at a minimum every four hours.*
- D8.2 Freezers used for CB unit storage where CB units are not fully immersed in liquid nitrogen shall have a validated system to monitor the temperature continuously or record the temperature every four hours at a minimum.*
- D8.3 There shall be a validated mechanism to consistently maintain levels of liquid nitrogen in liquid nitrogen freezers.*

**Explanation:**

The temperature of refrigerators and freezers must be monitored. If continuous monitoring is used, the system of monitoring must be validated. If continuous monitoring is not used, the CBB must record the temperature of refrigerators and freezers, or if CB units are fully immersed in liquid nitrogen, a mechanism must exist to consistently maintain levels of liquid nitrogen at the appropriate level.

**Evidence:**

Validation and qualification records demonstrating that the systems in place are capable of monitoring storage temperatures either continuously or at a minimum of every four hours should be available for review by the inspector.

Electronic or hard copy records of ongoing temperature monitoring of refrigerators and freezers must be available. For CB units stored fully immersed in liquid nitrogen, procedures detailing the system for maintenance and/or records of liquid nitrogen levels must be available.

**Example(s):**

Examples of temperature monitoring records may include but not be limited to:

- Temperature graphs – electronic or hard copy,
- Chart recorders, and/or
- Direct observation readings.

**STANDARD:**

*D8.4 Alarm Systems.*

- D8.4.1 Storage devices for CB units, reference samples, retention samples, and maternal samples shall have validated alarm systems that are continuously active.*
- D8.4.2 Alarm systems shall have audible and visible signals.*
- D8.4.3 Alarm systems shall be checked periodically for technical function. The records of such checks shall be maintained.*
- D8.4.4 The alarm system shall be capable of notifying designated personnel 24 hours a day.*

**Explanation:**

The designated personnel must be trained in handling the alarm and steps to take in the event that CB units must be salvaged. Notification should be designed in a cascade fashion, so that failure to notify the first designated person will trigger notification of second one and so on. A sufficient number of persons should be designated so that the likelihood of failure of the entire cascade is reduced to a minimum. The cascade notification procedure should be periodically checked, preferably outside regular hours and in an unannounced way, to verify proper function and time required to notify one of the designated people.

**Evidence:**

Records of such checks demonstrating a sufficient notification procedure should be maintained.

**STANDARD:**

*D8.4.5 Alarm parameters shall be set to allow staff sufficient time to salvage CB units, reference samples, retention samples, and maternal samples.*

**Explanation:**

Alarms must not be set at the lowest possible temperature that CB units and samples can be stored without detriment to the biological materials. The temperature and/or liquid nitrogen levels at which an alarm is set must allow staff time to correct the situation or transfer contents to alternative storage.

**STANDARD:**

*D8.4.6 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.*

**Explanation:**

Alarm parameters include lower and upper limits that would trigger the alarm. These limits should be outside the acceptable temperature ranges set by the CBB. This should allow time to address the freezer malfunction in time to prevent CB units from becoming unsuitable for administration due to warming events. It is understood that extenuating circumstances may prevent all CB units and/or samples from being salvaged, but the CBB must make reasonable attempts to devise a plan to salvage as many as possible.

The instructions must include a procedure for notifying designated staff and an outline of the procedures to follow to maintain the CB units at safe temperatures.

**Evidence:**

Alert and alarm levels should be defined within the relevant policy or operational procedure.

**STANDARD:**

*D8.4.7 Any alarm event and its resolution shall be documented.*

*D8.5 Contingency plans or storage devices of appropriate temperature shall be available for maintaining CB units, associated samples, reference samples, retention samples, and maternal samples at the storage temperature in the event the primary storage device fails.*

**Explanation:**

In the event of primary storage device failure, there must be a procedure in place to maintain CB units at the specified storage temperature.

**Example(s):**

Steps to take until the device is fixed or replaced may include:

- Transfer CB units to back-up freezers,
- Transfer units to another facility,
- Place units in dry shippers, and/or
- Manually top freezers with liquid nitrogen.

**STANDARD:**

*D9 DISPOSITION*

*D9.1 The CBB shall have a policy regarding the disposition of a CB unit, including at a minimum:*

*D9.1.1 CB units released for clinical use.*

**Explanation:**

The CBB must have a policy for qualifying CB units for clinical use. This includes listing the specifications of the CB unit.

**Example(s):**

The U.S. FDA Guidance Document, “*Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*” lists required specifications for CB units to be licensed. These criteria may also be useful for CBBs not necessarily requesting FDA licensure. This table is available at

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf>.

Table A. Required and Recommended Tests and Test Results <sup>1</sup>

Product Characteristics <sup>2</sup>	Testing	Sample (Type and Timing)	Results of Product Testing
Safety	Infectious diseases – Testing Required. (21 CFR 1271.45 through 1271.90)	Maternal peripheral blood obtained within 7 days of cord blood collection – Type and Timing Required. (21 CFR 1271.80(a) and (b))	All tests negative except non-treponemal test for syphilis when confirmatory test is negative. (Cytomegalovirus (CMV) results are recorded).
			CMV - Report
	Sterility - Bacterial and fungal cultures – Testing Required. (21 CFR 211.165(b), and 21 CFR 610.12)	HPC-C (pre-cryopreservation) *	No growth
	Hemoglobin	Cord blood** or appropriate donor sample obtained at time of cord blood recovery	No homozygous hemoglobinopathy
Purity and Potency <sup>3</sup>	Total nucleated cells (TNC)	HPC-C (pre-cryopreservation)	$\geq 5.0 \times 10^5$ TNC ***/ unit HPC-C
	Viable nucleated cells	HPC-C (pre-cryopreservation)	$\geq 85\%$ viable nucleated cells
	Viable CD34+ cells (flow cytometry)	HPC-C (pre-cryopreservation)	$\geq 1.25 \times 10^6$ viable CD34+ cells ****/ unit HPC-C
Identity	Human leukocyte antigen (HLA) Typing	Cord blood	Report
	Confirmatory HLA typing	Attached segment of HPC-C	Confirms initial typing
	Blood Group and Rh Type	Cord blood	Report

<sup>1</sup> Testing, Sample (Type and Timing), and Results are recommended unless specifically noted as required.

<sup>2</sup> The PHS Act requires a demonstration that the product is safe, pure, and potent.

<sup>3</sup> Other purity and potency assays may be considered under the BLA

\* Sample may be obtained before or after addition of the cryoprotectant.

\*\* Cord blood = a sample of unmanipulated cord blood. A red cell sample or other cord blood aliquot obtained after volume reduction may be used for testing with appropriately validated reagents or test systems.

\*\*\* Based on 20 kg recipient, a target dose of  $\geq 2.5 \times 10^7$  nucleated cells/kg and  $\geq 70\%$  post-thaw recovery =  $1.7 \times 10^7$  nucleated cells/kg.

\*\*\*\*Based on CD34+ cells  $\geq 0.25\%$  of TNC prior to freezing.

**STANDARD:**

- D9.1.2 CB units used for research.*
- D9.1.3 CB units used for quality assurance activities.*
- D9.1.4 CB units that are discarded.*
- D9.2 Nonconforming CB units.*
  - D9.2.1 The CBB shall have a policy for the management of CB units that are not accepted into inventory.*
  - D9.2.2 The CBB shall have a written policy for the management of CB units that do not meet in-process or final unit endpoints and/or specifications.*
  - D9.2.3 The CBB shall have a written policy to address positive or indeterminate results found during the screening process and/or laboratory testing of reference samples or maternal samples.*

**Explanation:**

Nonconforming CB units do not necessarily have to be discarded. There are uses for units for reasons other than clinical administration. For public banking, CBBs will be required to adhere to all regulatory requirements regarding inclusion/exclusion criteria, as covered by applicable regulatory agencies. Since related banking is a contractual service, the private CBBs may be more tolerant of acceptance issues than a public CBB. A cryopreserved TNC count may have a lower threshold at a private bank than what is acceptable at a public bank. These criteria should be well documented and explained to the prospective cord blood donor. Issues related to incorrect labeling or inappropriate labeling that make unit identity questionable should be an exclusion criterion at all banks.

If a CBB elects to retain a nonconforming CB unit, it must clearly distinguish the unit from the general inventory.

**Example(s):**

Alternative uses for nonconforming uses include research, quality control, or exceptional release for underrepresented populations.

**STANDARD:**

- D9.3 Disposal.*
  - D9.3.1 There shall be a policy outlining personnel authorized to discard CB units.*

**Explanation:**

The disposition of a CB unit impacts the level of oversight necessary for CB unit disposal.

**Example(s):**



Disposal of a CB unit accepted into inventory may require approval from key personnel, whereas a CBB may choose to allow processing personnel to discard units that do not meet volume thresholds.

**STANDARD:**

*D9.3.2 The records for discarded CB units shall indicate the unique numeric or alphanumeric identifier of the CB unit; the reason, date, and method of disposal; and the individual who disposed of the CB unit.*

*D9.3.3 For related CB unit disposal:*

*D9.3.3.1 Disposal shall comply with the terms of disposal in the written agreement.*

**Explanation:**

Disposal of related CB units must be highlighted in the informed consent or documented in the agreement with the family. This discussion must include the facility's policies for disposal and the family's options for alternative storage.

**Evidence:**

A copy of the informed consent or written agreement should be included with the disposal documents.

**Example(s):**

Approaches to dealing with related disposal include:

- Contacting the CB unit donor or prospective recipient, if alive,
- Obtaining informed consent from the biologic mother or legal guardian in accordance with Applicable Law in the case of a minor donor or prospective recipient,
- Contacting the family member with whom the original contract/consent to collect and store the CB unit was made, or designee, and/or
- Transferring the CB unit to another facility if consent to dispose is denied.

The discussion regarding disposal may also occur in consultation with the prospective recipient's physician.

In the instance where there is no longer a family need for a CB unit that otherwise meets unrelated allogeneic CB banking criteria, the family may be offered the opportunity to release the product into a CBB's unrelated allogeneic inventory. This consent for release must be documented and must follow Applicable Law.

**Explanation:**

Issues regarding alternative storage should be explained during the informed consent process. Examples of issues include if the CB unit must be transferred to a CBB for continued related banking or if the CB unit can be crossed over to an inventory for research or unrelated allogeneic use. If a CB unit is to be crossed over, the CB unit must have met all unrelated allogeneic requirements at the time of collection and processing. Other issues include transportation, financial responsibilities, and who is responsible for arranging the alternate storage.

If the CB unit is donated for research, the CBB should document to what institution the CB unit was transferred, the transfer agreement, and institutional approval for using the CB units for specific research. The maternal donor must clearly give her consent if the CB unit is to be used for research. If the CB unit is sold for commercial use, this also must be disclosed to the mother.

**STANDARD:**

*D9.3.3.2 Reasons for disposal and the process of notification shall be identified at the time of the written agreement.*

**Evidence:**

Appropriate documentation demonstrating reasons for disposal shall be included with the disposal records.

**Example(s):**

Rationale for discarding a CB unit may be related to the following:

- Delivery issues/complications,
- Inappropriate donor screening results (risk factors, family health history),
- Compromised collection bag integrity,
- Incomplete or inappropriate labeling,
- Positive infectious disease testing,
- Inappropriate quality control indexes,
- Processing issues, or
- Low TNC or volume.

**STANDARD:**

*D10 CORD BLOOD UNIT TESTING*

*D10.1 The CBB shall define tests and procedures for measuring and assaying CB units to determine their safety, viability, and integrity and to document that units meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the CB unit.*

*D10.2 Testing control procedures shall include:*

*D10.2.1 The use of established and validated assays and test procedures for the evaluation of the CB unit.*

*D10.2.2 Adequate provisions for monitoring the reliability, accuracy, precision, and performance of test procedures and instruments.*

*D10.2.3 Adequate identification and handling of all reference samples so that they are accurately related to the specific CB unit being tested, to its infant donor, the infant donor's mother, and to the specific recipient, as applicable.*

*D10.2.4 Verification of new reagent lots to provide comparable results to*

*current lots or give results in agreement with suitable reference ranges before or with placement into service.*

*D10.2.5 Where available, use of reference or quality control material demonstrated to give results within the defined range established for that material.*

*D10.2.6 Functional checks performed for testing instruments, as appropriate, prior to testing reference samples, maternal samples, or recipient samples.*

*D10.2.7 Documentation of ongoing proficiency testing as designated by the CB Processing Facility Director. The results shall be reviewed by the CB Processing Facility Director or designee and outcomes reviewed with the staff and representatives from the QM Program, if applicable.*

**Explanation:**

CB Processing Facility controls are procedures that support processing and characterization of CB units. They are to be scientifically sound, i.e., based on logical, validated, and referenced practices. Processing does not end when the CB unit is put in the freezer.

**Example(s):**

It is recommended that viability and potency should be demonstrated after cryopreservation and storage to confirm the integrity of the CB unit. Caution must be used in interpreting traditional viability tests; however, as their accuracy is limited by the stage of cellular repair after thaw.

**STANDARD:**

*D10.3 CB units shall be tested as outlined in the Testing Requirements table in Appendix IV.*

**Explanation:**

Appendix IV outlines the tests that are required, including when the tests must be performed and on what sample. Specific requirements for some individual tests are specified later in this section.

The nucleated red blood cell count (NRBC) must be reported. However, CB units that were processed prior to this requirement may not have enumerated this population of cells. Rubinstein, et al, reported that NRBC dose predicted speed of engraftment; therefore, inclusion of NRBCs in the Total Nucleated Cell (TNC) count does not reduce the effectiveness of the post processing TNC count as an index of the quality of a CB unit as a graft. The correlation between the number of NRBCs and the number of HPC probably reflects the involvement of early stem cells in erythroid responses (Blood. 2002 Oct 1;100(7):2662-4). However, the CBB must clarify the contribution of NRBC to the nucleated cell population for the Clinical Program to facilitate an informed donor selection. Additional parameters of the blood count should be reviewed to exclude congenital neutropenia, thrombocytopenia, and immune deficiency.

ABO/Rh typing provides important information to the Clinical Program with regard to blood product support of a recipient post-transplant. This typing also affords a means of CB unit identification both in the CBB and at the Clinical Program.

Because societies are becoming more integrated and abnormal red blood cell diseases are carried by populations previously considered unable to transfer or be affected by them, hemoglobinopathy testing must be performed regardless of the family's ethnic background or history. The screening test must utilize a method that distinguishes hemoglobin A, A2, S, C disease and/or trait. Testing for alpha and beta thalassemia is recommended if indicated. CB units homozygous for either sickle cell disease or thalassemia will be deferred. CB units heterozygous for either sickle cell trait or thalassemia will be accepted and distinguished as such; CB units heterozygous for both sickle cell and thalassemia trait will be deferred. Testing may either be performed on residual red blood cell material remaining post-processing or on a sample of whole CB prior to processing. Newborn screening is also acceptable. A positive test is defined as the presence of a homozygous hemoglobinopathy, e.g. Hgb SS (SA in fetus), or double trait on the same gene (e.g. SC or Sbeta Thal). The presence of a single trait is not an exclusion. The presence of two traits on different genes (e.g. alpha Thal trait and beta Thal trait) is not necessarily an exclusion and should be evaluated by the CBB Medical Director.

Though testing based on intact cell membranes and active cell metabolisms that exclude Propidium Iodide (PI), 7-Amino-Actinomycin D (7-AAD), or trypan blue dyes are commonly used to assess viability, CFUs are grown from functionally viable cells and increase confidence in CB unit quality and ability to engraft. The term "CFU" is used generically and the CBB may choose to test for total CFU or CFU-GM. If the CBB only performs GM assays, this must be communicated to the Clinical Program.

If CB infectious disease testing is not performed by the CBB, CB serum or plasma must be retained for use in future testing. Testing the CB unit for infectious diseases adds a dimension of safety. Infectious disease testing of the maternal samples is understood to be a surrogate test, and strongly reflective of the infectious status of the CB unit since the circulation is shared during gestation. Infectious disease testing is performed on a maternal sample collected within seven days before or after delivery, generally with results available prior to release to inventory.

**Evidence:**

Results of infectious disease tests are part of the CB unit record and are reported to the Clinical Program. Although it is not necessary to identify the particular test in the CB unit record, CBB documents should be able to trace the method and even the version or generation of the test used for testing. When used for testing reference samples, CB Processing Facilities in the U.S. should indicate that results were obtained from tests not yet approved by the FDA for these purposes.

**Example(s):**

Unless otherwise specified in Appendix IV or in the Standards, the testing can be performed anytime as long as it meets the minimum requirements in the table. For example, microbial cultures must be performed between processing and cryopreservation, but ABO/Rh testing can be performed any time before listing the CB unit, even at the time of collection.

Examples of validated potency assays may be CFU, viable CD34, or some other functional assay. Currently, there is no standard for potency testing in the field. The U.S. FDA published draft guidance on potency testing in October 2008 titled, "Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products." This guidance can be found on the FDA website at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072571.htm>.

In the U.S., state and reference laboratories have standards for hemoglobinopathy testing. Diagnostic tests including HPLC, isoelectric focusing, or electrophoresis are appropriate, while SICKLEDEX or rapid testing assays such as those used in Transfusion Medicine laboratories are not. The CB Processing Facility Director must confirm that procedures used are appropriate.

If performed on a sample obtained prior to cryopreservation, it is recommended to perform CFU or another validated potency assay from a frozen segment prior to release to determine the effect of cryopreservation and storage. Typically, laboratories use methylcellulose media to discriminate all colony types but it is acceptable to assess GM or any other validated method whose ranges are described in the facility's policies and procedures.

Infectious disease testing of the CB unit is recommended by these Standards though it is understood that many kits are not FDA-approved for this specimen. Clinical Programs in the U.S. are interested in their liability regarding use of CB units. If testing is performed but not FDA approved, a CBB can report results with notation that this assay is not yet approved in these circumstances by the FDA.

For more information regarding donor eligibility determinations based on donor screening and testing for relevant communicable disease agents and diseases (RCDADs), refer to the FDA's Guidance for Industry for Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm>.

For a list of FDA approved donor screening tests, refer to <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm>.

CB unit infectious disease testing is required by the European Health Ministry and must be performed prior to importing a product to a European country, either by the CBB or by submitting samples to the Clinical Program. CBBs should submit a list of locally required tests and the menu of infectious disease tests performed by their laboratory in the application process. Inspectors must note if the CBB is following its specific national requirements.

If required, CB unit infectious disease testing can be performed at the same time or can be deferred until the CB unit is requested for transplant. Alternatively, samples retained by the CBB can be transferred to the Clinical Program for testing in its own facility.

Testing maternal donors for CMV is required; however, testing the CB unit for CMV is optional. Transplant patients typically receive many blood products in support of their therapies and exposure to CMV is related to the frequency of transfusion. There are a variety of ways that CBBs address testing for CMV. Often, CMV is included in the infectious disease panel offered by the CBB's infection disease testing laboratory. Total antibody including IgG and IgM can be tested on maternal samples, and CB samples may be tested for IgM when maternal samples are positive. CMV PCR is available in some labs.

## **STANDARD:**

*D10.3.1 CBC with differential testing shall include enumeration of neutrophils, lymphocytes, monocytes, and platelets. Parameters for each shall be defined.*

**Explanation:**

A differential is obtained to screen for the presence of inherited blood dyscrasias.

**Example(s):**

Congenital **neutropenia** (Kostmanns Syndrome) would be suspected if the neutrophil count was low (e.g. <10%) or the absolute neutrophil count was calculated to be below 1,500/uL (% neutrophils +% bands x total WBC/uL). A screen for **lymphopenia**, which could be a sign of severe combined immunodeficiency syndrome or another inherited complex immunodeficiency syndrome, should be conducted. The absolute lymphocyte count should be 1,500/uL or greater (% lymphs x WBC/uL). In the absence of neutrophils or lymphocytes or with maternal cell engraftment, **eosinophilia** may be prominent. If eosinophilia (>10%) is present, an investigation should occur. Extreme **anemia**, in the absence of known bleeding, is also a potential sign of a congenital red cell dyscrasia. Pure red cell aplasia (Diamond-Blackfan Anemia) and alpha thalassemia can both present in the newborn period. In the case of DBA, the MCV will be very high, while in the case of alpha thalassemia, the MCV will be very low (<90). **Thrombocytopenia** (platelets <100K/uL) may be a sign of congenital thrombocytopenia (megakaryocytic thrombocytopenia, thrombocytopenia with absent radius, fanconi anemia). If any of these abnormalities are present, further investigation should occur. If investigation is not possible, the unit should not be listed on a donor registry or made available for transplantation. In some cases, notification of the baby's physician could help identify a baby at risk for the clinical problems associated with these inherited diseases.

**STANDARD:**

*D10.3.2 Microbial cultures shall be performed using a system validated for the growth of aerobic and anaerobic bacteria and fungi.*

*D10.3.2.1 CB units for unrelated use shall be free from microbial contamination.*

*D10.3.2.2 For related CB units, the results of positive microbial tests shall include identity and sensitivities of the organism(s). These results shall be reported to the prospective Clinical Program.*

**Explanation:**

Unrelated CBBs do not list, or make available, CB units that have demonstrated microbial growth, though in related programs, culture-positive CB units may be retained. Unrelated CB inventories established prior to these Standards may have retained CB units demonstrating bacterial growth. These units should be stored in the vapor phase of liquid nitrogen in order to reduce the risk of contamination to other stored CB. If a culture-positive product is distributed, the CBB must disclose the sensitivities to the Clinical Program.

The nature of the delivery process suggests that a level of culture positivity can be expected. The CB Processing Facility should establish acceptable positivity rates to determine when internal thresholds have been exceeded and when action should be taken.

Antimicrobial sensitivities refer to aerobic bacteria, anaerobic bacteria, and fungi. In the related banking setting, the CBB Medical Director need not authorize CB units for release unless considered for use in transplantation. A positive microbial test may not preclude a related CB unit from being infused, so long as the transplant physician and recipient are informed. However, the CBB Medical Director must still review CB unit parameters before releasing the CB unit according to pre-determined criteria, whether internal or as defined by the transplant physician.

Microbial cultures must be obtained from a sample representative of the final CB product after processing. The CBB must validate bacteriological cultures.

**Example(s):**

The cultures of each can either be obtained together after processing or be obtained separately via the CBB's process of qualifying the cryopreservation media. Culture inoculum may be obtained from:

- Post-processing byproduct where manufacturer volume recommendations can be fulfilled,
- Final product prior to cryopreservation with cryoprotectant,
- Final product prior to cryopreservation without cryoprotectant, or
- Cryoprotectant material(s) as additional safeguards relating to reagent sterility:
  - Single use vials, or
  - Tested multi-use vials.

Validation of a CBB's method of detecting microbial contamination can be achieved by equivalency studies, serial dilutions, or reference to published sources in accordance with Applicable Law.

For the purposes of these Standards, sterility testing is defined as the process used to screen for the presence of microbes, as required by this Standard, and is equivalent to the European Union's requirement to screen for microbial contamination.

**STANDARD:**

*D10.3.3 HLA Class I and Class II typing shall be performed by DNA-based methods.*

**Explanation:**

If a CB unit is stored for related use and not tested upon storage, HLA typing must be determined and compared with donor typing prior to release. Before listing an unrelated CB unit, typing must include a minimum of two digits, which must be included when listing a CB unit.

A minimum of two digits from DNA-based HLA typing is required to list a CB unit for search. The rationale for allowing only two digits at the time of listing is because this approach is sometimes used as a cost-control issue. However, to help ensure the appropriate selection of a CB unit, the CBB must perform high resolution typing (four digits) for DRB1 before actually releasing a CB unit for administration. These Standards require high resolution typing (four digits) of DRB1 before releasing the CB unit to the Clinical Program. As outlined in Appendix IV, only two digits for DRB1 are required to list a CB unit, but high resolution typing (four digits) is required before releasing the CB unit to the Clinical Program.

**Example(s):**

Though not required, it is highly recommended that four digits are included when listing the CB unit in order to provide Clinical Programs with enough information to make a selection in minimal time.

**STANDARD:**

*D10.4 Test results that are positive or outside of the established range and are relevant to the donor's health shall be communicated to the infant donor's mother or legal guardian and/or her physician according to Applicable Law and CBB policies and Standard Operating Procedures.*

**Explanation:**

CBBs must give hemoglobinopathy screening results to the infant donor's mother or legal guardian and/or the physician in accordance with Applicable Law. Some laws may prohibit this reporting, while others may require it.

**STANDARD:**

*D11 MATERNAL TESTING*

*D11.1 The maternal blood sample obtained within seven (7) days before or after collection of the CB unit shall be tested for evidence of infection as outlined in the Testing Requirements table in Appendix IV utilizing assays required for volunteer blood or tissue donations and according to Applicable Law.*

**Explanation:**

Maternal serologic and NAT testing is an appropriate surrogate for representing the infectious status of the cord blood (CB) unit for a number of reasons. While admittedly conservative, this approach enhances protection of CB unit inventories and recipients. The placenta is an effective barrier for disease agents but the extent of vertical transmission is not completely consistent. Furthermore, reference samples may be inadequate due to dilution with anticoagulant and processing reagents. Many infectious disease testing technologies have not been approved for CB specimens in various countries.



This standard defines the minimal evaluation for infectious agents. For CB units in the U.S, laboratories must use approved, cleared, and/or licensed donor screening tests for tissue donors, according to manufacturers' instructions. Testing must be performed in labs certified to perform these tests under CLIA or equivalent requirements as determined by CMS. Similarly, in other countries, the testing and laboratory requirements are specified by the national competent authority. For European Union member states, the tests must be carried out by a qualified laboratory, authorized as a testing center by the competent authority in the Member State, using CE-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

Infectious disease panels may change due to emerging pathogens. It is expected that CBBs include detection of agents based on significance for their location and donor population. Other communicable disease tests should be added to the donor evaluation as they become available and recommended to increase the product safety. Testing for additional infectious agents may be included by governmental regulation as they become a global or community health care issue.

West Nile Virus transmission from infected donors has been confirmed in recipients of blood components and solid organs. This transmission has resulted in subsequent infection and death of the recipient. Testing results may influence the timing of recipient conditioning (when using autologous or allogeneic donors) or lead to selection of an alternative donor when possible.

CMV testing may be required by national competent authorities. In the U.S., CMV Total antibody testing is required on a maternal sample, using an FDA-licensed, approved donor screening test.

Transfusion and/or replacement fluids given in significant amounts can dilute plasma. As required by Applicable Law, systems should be in place to prevent the collection of samples from maternal donors for infectious disease testing if significant infusion of blood or fluids has occurred.

When required, CBBs must report positive results within the specified timeframes.

**Evidence:**

Standard Operating Procedures in place define processes for performing testing within appropriate timeframes and with appropriate testing methods per Applicable Law and policies of the institution. Record reviews of charts and testing records support compliance with these requirements.

**Example(s):**

Testing records and SOPs demonstrate compliance, as defined by the institution and Applicable Laws. For outsourced testing, processes to monitor testing services of contracted testing labs are present.

The CBB may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease, as defined by Applicable Law. (For example, at the time of revision of these standards, FDA requires testing using donor screening test kits in a CLIA lab for HIV-1 and HIV-2 antibodies and HIV-1 NAT testing, as well as antibodies to HIV-1, Group O, unless HIV-1, Group O donor risk is appropriately evaluated during donor screening.) In addition, other testing for infectious transmissible agents may be required by Applicable Law

or implemented per institutional policy. Similarly, member countries of the European Union may amend and/or introduce additional testing requirements. (For example, per EU requirements, testing donors for antibody to Human T-cell lymphotropic virus, type I is required only for donors at risk. Additionally, testing strategies may include repeat serological testing after 180 days, NAT testing, testing of a sample of cord blood, or other testing requirements as defined by National Competent Authority.)

According to the FDA, relevant communicable disease agents and diseases (RCDADs) may be assessed through donor screening and/or donor testing. FDA intends to notify the industry through published guidance from time to time of any additional relevant communicable diseases and include methods (screening and/ or testing) by which those agents should be assessed. In making this determination, the factors considered in naming a disorder a “relevant communicable disease” are:

- There might be a risk of transmission through an HCT/P either to the recipient or to the staff handling the product because of the disease or disease agency. It is transmissible through HCT/P.
- It is sufficiently prevalent as to affect the potential donor population.
- There could be fatal or life-threatening consequences as a result of transmission.
- Effective screening mechanisms and/or an approved screening test for donor specimens have been developed.

**STANDARD:**

*D11.2 Positive or indeterminate test results, excluding cytomegalovirus, shall be communicated to the mother and/or her physician according to Applicable Law and CBB policies and Standard Operating Procedures.*

**Explanation:**

Maternal testing specimens are required to be drawn within seven days before or after delivery to reflect the infectious status of the surrogate host at the time of donation. Retesting maternal donors at six months is not practical in most CBB settings. Therefore, interpretation of indeterminate or repeatedly reactive test results is not conclusive. Since the risk of transmission remains, abnormal results are communicated to the donor and/or physician so that appropriate follow up can occur in light of the donor’s clinical presentation and history.

The rationale for reporting indeterminate results is to alert physicians and mothers of potential health related issues. Reporting to public health authorities is not necessary if confirmatory tests are negative.

Some abnormal testing results may be urgent and require the CBB to notify the donor or the donor’s physician to protect the health of the mother or infant donor.

**Evidence:**

The CBB must have defined parameters within their procedures that specify when to quarantine or discard these CB units and how abnormal test results are managed with regard to donor, physician, and public health notification. Records for abnormal test results, when traced to the mother and unit, demonstrate compliance with SOPs for disposition and management of the unit and notification of the donor, physician, and authorities per facility policy and Applicable Law.

Records should document that donors were tested for these infectious agents within the specified time period and that the results were obtained prior to the release of the CB unit.

**Example(s):**

An example of a potentially urgent finding could be a positive HIV test where immediately counseling a breast-feeding mother would be appropriate.

**STANDARD:**

*D11.3 All maternal samples should have negative or non-reactive test results with the exception of Cytomegalovirus antibody, Hepatitis B core antibody, and non-Treponema pallidum (syphilis) testing.*

**Explanation:**

The tests included in the standard can be positive or reactive as long as certain requirements are met; however, the CBB has the responsibility to confirm such exceptions are allowed by the Applicable Law and registries through which it lists unrelated CB units. Some registries may not allow exceptions.

**Evidence:**

Consistent with Applicable Law, SOPs define what, if any, reactive donor screening test results are acceptable for storage and release of a CB unit for infusion. (This is supported by the method and documentation required for such release.) Unit records support compliance with Applicable Law and facility policy for reactive test results.

**Example(s):**

If allowed by Applicable Law, many institutions may allow the use of CB units that are reactive/positive for anti-HBc, provided there is no other testing suggestive of Hepatitis B infection. SOPs should address disposition of units with reactive donor screening test results and include specifics for use of units with any reactive testing. Unit records should appropriately show disposal or non-clinical use for all results other than those allowed as exceptions and appropriate quarantine policies, consistent with facility-specific policy and Applicable Law.

**STANDARD:**

*D11.3.1 If allowed by Applicable Law, maternal samples that are Hepatitis B core antibody positive and are accepted shall be Hepatitis B Surface Antigen (HBsAg) nonreactive/negative by DNA testing and also negative by HBV DNA testing.*

**Explanation:**

In some countries, maternal samples that are hepatitis B core antibody positive may be accepted if they are hepatitis B negative by DNA testing. This standard applies to this situation where allowed by Applicable Law for CBBs that wish to salvage CB units that are hepatitis B core antibody positive. CBBs are not required to test for hepatitis B by DNA testing; they may reject all CB units that are hepatitis B core antibody positive rather than proceed to DNA testing. Although these standards allow for the retention of hepatitis B core antibody positive products when hepatitis B by DNA testing is negative, these abnormal testing results must be explicitly communicated to the Clinical Program prior to release.

**STANDARD:**

*D11.3.2 If allowed by Applicable Law, maternal samples that test positive for syphilis using a non-treponemal-specific screening test and are accepted shall be negative using a treponemal-specific confirmatory test.*

**Explanation:**

Non-specific syphilis donor screening testing such as RPR or VDRL testing may be associated with higher false reactive rates than those donor screening tests that are specific for treponema palidum. For example, as an exception, FDA allows a donor to be determined as eligible if an FDA-approved non-treponemal donor screening test is positive/reactive and a specific treponemal confirmatory assay (FTA-ABS) is negative, provided all other required testing and screening is negative/nonreactive.

**Evidence:**

With regard to syphilis testing, if CB units are retained for possible infusion, SOPs must be detailed enough to distinguish practices for treponemal versus non-treponemal donor screening testing and confirmatory assays so that policies can be evaluated against requirements of Applicable Law.

**Example(s):**

In the U.S., if a treponemal-specific screening test or a specific treponemal confirmatory test is positive, the CB unit cannot be labeled as eligible and remains in quarantine.

**STANDARD:**

*D11.4 If Applicable Law and CBB policies and Standard Operating Procedures allow release of CB units from quarantine where the maternal samples are positive/reactive for Hepatitis B core antibody and/or non-treponemal syphilis, the CBB must have a written procedure that describes the documented notification of relevant results to the Clinical Program prior to release for administration.*

**PART E: CORD BLOOD LISTING, SEARCH, SELECTION, RESERVATION, RELEASE, AND DISTRIBUTION STANDARDS**

**STANDARD:**

**E1 GENERAL REQUIREMENTS**

- E1.1 There shall be designated facilities of adequate design and location that prevent mix-ups, mislabeling, or other errors in the procedures related to CB unit listing, search, selection, reservation, release, and distribution.*
- E1.2 There shall be a defined process to prevent listing of related CB units for unrelated use.*
- E1.3 The CBB shall have policies and Standard Operating Procedures for the following at a minimum:*
- E1.3.1 Listing, search, selection, reservation, release, and distribution of CB units to Clinical Programs.*
  - E1.3.2 Verification of HLA typing of the CB unit.*
  - E1.3.3 Verification that the infant donor and the recipient are different individuals in the case of complete HLA matches.*
- E1.4 If the CBB utilizes a registry, the CBB shall use a validated process for uploading CB unit information to the registry.*

**Explanation:**

Registries include entities that perform search and match functions and listing organizations.

**STANDARD:**

- E1.5 The CBB or registry shall have a validated electronic record system that enables search and match operations and reporting of results within a defined timeframe.*
- E1.5.1 If an outside agency is used for search and match functions, its electronic record system shall meet these Standards.*

**Explanation:**

This may be as simple as having an established relationship with a registry. However, if multiple registries are populated by the CBB inventory data or if the CBB performs internal searches, then there must be systems in place to confirm that CB units are appropriately removed from inventory at the time of reservation and/or release.

The CBB should validate the process for listing, search, selection, reservation, release, and distribution to document that the process properly identifies the CB unit and protects unit integrity.

The electronic record system's algorithm must be validated to list CB units properly when performing recipient searches against the registered inventory.

**Evidence:**

The CBB should show the inspector written agreements between the CBB and registry that describe the registry's responsibilities.

**STANDARD:**

*E1.6 The CBB or registry shall have policies and Standard Operating Procedures for the reservation and allocation of CB units.*

*E1.6.1 Reservation of a CB unit shall not be in place simultaneously for more than one potential recipient.*

*E1.6.2 The CBB shall notify all registries in a timely manner when a CB unit is removed from inventory.*

**Explanation:**

It is important that the reservation system have the capability to remove CB units from searches or identify them as unavailable for transplant if they are being evaluated and/or used for transplant to another patient. If CBBs share their listing with multiple search engines, or also perform searches locally, there must be a process that updates all search lists from that CBB.

**STANDARD:**

*E2 REVIEW AND LISTING OF CORD BLOOD UNITS*

*E2.1 The CBB shall have policies and Standard Operating Procedures for the comprehensive review of CB unit records prior to listing a CB unit, including at a minimum:*

**Explanation:**

The CBB shall assess the safety of CB units prior to making them available for human use. Even if a family is considering the use of a related CB unit, the transplant physician may want to compare it to unrelated CB units prior to treatment in case a better choice is available. A better comparison (and, consequently, better results) is only possible if all the available information is the same.

**Example(s):**

The information that must be reviewed prior to registering a CB unit is listed in the following Standards. The details for each are provided in Part D.

**STANDARD:**

- E2.1.1 *Results of tests outlined in the Testing Requirements table in Appendix IV.*
- E2.1.2 *Infant donor's ethnicity/race.*
- E2.1.3 *Infant donor's gender.*
- E2.1.4 *Infant donor's physical examination.*
- E2.1.5 *Maternal risk factors for transmission of communicable disease.*
- E2.1.6 *Family medical history for transmissible genetic and malignant diseases.*
- E2.1.7 *Hemoglobinopathy, if known.*
- E2.1.8 *Consents.*
- E2.1.9 *Processing and cryopreservation parameters.*
- E2.2 *Unrelated CB units shall be made available for search on a registry and/or the CBB's inventory only after testing and medical review has been completed and a representative(s) of the QM Program has reviewed the CB unit records.*

**Explanation:**

In addition to review by the CBB Medical Director or designee, someone from quality management must review the CB unit records and approve the unit's release. If there are discrepancies between the medical and quality reviews, they must be resolved prior to listing the unit.

**STANDARD:**

- E2.3 *The nature of nonconforming CB units shall be disclosed to the registry.*

**Example(s):**

Examples of nonconforming CB units include:

- Units obtained before initial FACT-NetCord accreditation,
- Units without an attached segment,
- Units with an incomplete maternal health questionnaire, and
- Units with positive infectious disease markers.

**STANDARD:**

- E3 *CORD BLOOD UNIT SELECTION AND RELEASE FOR ADMINISTRATION*

- E3.1 *The CBB shall retain indefinitely documentation of requests for CB units, requests for reference samples and maternal samples, requests for and results of testing, and transportation and shipping of CB units and samples between facilities.*
- E3.2 *The CBB shall have a system to prevent a CB unit from being reserved for a single patient by more than one transplant center at a given time.*

**Explanation:**

A CBB needs to be able to confirm that the information provided to the Clinical Program or to the registry(ies) is correct and complete. Components of this system need to account for duplicate searches by several Clinical Programs or registries, blocking of reserved CB units from further requests, and removing CB units from reserved status. If CB units are in multiple registries and in an internal release program, there must be a mechanism for the CBB to inform all involved registries of change in CB unit availability status.

**STANDARD:**

E3.3 *Before a CB unit is released, a sample obtained from a contiguous segment of that CB unit shall be tested to verify HLA type and, if possible, cell viability. Verification typing shall be performed at least once after a CB unit is cryopreserved.*

E3.3.1 *If a contiguous segment was never available, another validated method shall be used to identify the CB unit.*

E3.3.2 *Any histocompatibility discrepancy shall be resolved and communicated to the registry and the Clinical Program.*

E3.3.3 *Where proof of identity has been obtained for the CB unit, a copy of the report shall be provided to the Clinical Program upon request for the CB unit.*

**Explanation:**

Repeat HLA typing, including typing of a sample from a contiguous segment, is a check of CB unit identity as well as a verification of the HLA type. The second testing may have been performed at the time of the CB unit's entry into inventory or prior to CB unit release. Verification testing need not be performed with every request for a CB unit. It is sufficient that HLA typing is confirmed one time from an integral segment and the results made available in the information relayed to each Clinical Program interested in that CB unit.

If a contiguous segment is not available for older units banked prior to FACT-NetCord accreditation, there must be an approach defined by the CBB to confirm CB unit identity prior to release. In addition, the Clinical Program must be notified well in advance so plans can be made to continue or decline further pursuit of this CB unit.

**Example(s):**



If the volume of a segment allows only a small amount of DNA to be extracted, it may be acceptable to perform a broad range of HLA typing on a non-contiguous reference sample and then verify this typing by a more limited panel of HLA tests performed on the contiguous segment. Other additional genetic markers, such as short tandem repeats (STRs), can also be used to confirm identity.

**STANDARD:**

*E3.4 At the time of selection for administration, the CBB and/or registry shall provide all technical data to the Clinical Program, including at a minimum:*

**Explanation:**

The information that must be provided is listed below. All of this information may not be included on the registry, but the CBB must keep the information in a way that allows it to provide it to the Clinical Program upon selection. The CBB may also delegate this task to a registry, if used.

**STANDARD:**

*E3.4.1 Results of tests outlined in the Testing Requirements table in Appendix IV.*

**Explanation:**

CB unit characteristics must be obtained prior to cryopreservation. Older CB units may not have nucleated red blood cell testing, CD34 results, or CFU testing completed. The CBB must have a process to notify the Clinical Program that this testing was not performed. For old CB units, if the CFU are determined on a contiguous sample, the CBB has to communicate to the Clinical Program that the CFU number assigned to the CB unit is estimated from the results of the CFU number detected in the contiguous segment.

Using a contiguous segment to verify CB unit identity through HLA typing of a CB unit is considered critical to patient safety. Older inventory CB units may not have contiguous segments. These CB units may be available for search and used for administration; however, the CBB must have a process to notify the Clinical Program that segment testing is not available.

When confirmatory HLA typing is performed, the CBB must obtain, review, and archive the results. These results may be used in the future to support the identity of the CB unit and sample when offering the CB unit to another Clinical Program. Clinical Programs must be given past typing results in addition to current results. This is particularly relevant to older CB units where the original typing may be incorrect or new replication forks or “splits” have been identified. Registries often do not contain all historical results, but the CBB must still provide this information to the Clinical Program at the time of selection. The Clinical Program needs the opportunity to see this information before making a final decision about the quality of the CB unit.

At most, a CB unit has two to three segments from which to perform confirmatory and viability testing. Practically speaking, if a CB unit is considered for transplant on multiple occasions resulting in multiple requests for samples, all sources of cells for testing could conceivably be used.

While DNA-based typing up to two digits is required to list a CB unit, high-resolution typing (four digits) for DRB1 is required at the time of releasing a CB unit to a Clinical Program.

**Example(s):**

Samples of DNA are acceptable alternatives to segments for distribution to Clinical Programs for further testing.

Given the limited number of contiguous segments and amount of CB unit available for testing, if the CB unit has been previously evaluated for another potential recipient, that second testing is sufficient to fulfill this requirement. Viability can also be used; however, conditions of storage since the previous testing must be considered.

**STANDARD:**

*E3.4.1.1 For related CB unit administration, antimicrobial sensitivities shall be provided if positive microbial tests are documented in the CB unit record.*

**Explanation:**

It is understood that related CB units may be stored despite having positive microbial cultures. It is important that the Clinical Program and the patient be aware of culture results.

Specific unrelated donor eligibility requirements do not apply to related donors. However, if product testing (including microbial testing of the product) is performed, positive test results received on the CB unit should be reported in the summary of records.

**STANDARD:**

*E3.4.2 Gender of the infant donor.*

*E3.4.3 Risks of communicable and/or genetic diseases disclosed by the maternal medical and genetic screening or clinical chart review and the results of any investigation or further testing performed.*

*E3.4.3.1 For related CB units, history of malignant or genetic disease in a first degree relative of the infant donor shall be disclosed to the Clinical Program.*

**Explanation:**

Even if the risk has been excluded, the CBB must still disclose history of malignant disease in a first degree relative to the Clinical Program.

**STANDARD:**

*E3.4.4 The method of CB unit processing.*

*E3.4.5 Any variances in collection, processing, testing, cryopreservation, storage, and/or transport or shipping procedures that may influence the integrity and/or quality of the CB unit.*

**Explanation:**

This should include whether there is red cell and/or plasma depletion, name and volume of solutions added to the CB unit during processing, and freezing technique. Any risk or variance as determined by the CBB that may influence the selection decision by the Clinical Program must be communicated early in the search process so that the patient treatment plans are not adversely impacted.

**STANDARD:**

- E3.4.6 Physical characteristics of the CB unit, including at a minimum the number and type of bags or compartments used for storage.*
- E3.4.7 Information about the type of cassette the CB bag will be shipped in.*
- E3.4.8 Information about storage of the CB unit.*
- E3.4.9 Instructions for thawing and administering the CB unit.*

**Explanation:**

The intent of this standard is to communicate storage expectations to the receiving facility so they can be prepared to hold the CB unit in the appropriate manner prior to infusion. Providing the physical dimensions of the bag and canister may be helpful to the receiving facility in determining the storage location of the CB unit.

**STANDARD:****E4 CORD BLOOD UNIT DISTRIBUTION TO A CLINICAL PROGRAM**

- E4.1 The CBB shall obtain in written or electronic form a request from the transplant physician, designee, or registry for distribution of the CB unit prior to release of the product.*
- E4.2 The CBB Medical Director or qualified designee and a representative(s) from the QM Program shall conduct a comprehensive record review prior to distribution of a CB unit to a Clinical Program and document this review in accordance with Applicable Law.*

**Explanation:**

Distribution includes the transportation or shipping of a CB unit. The review required in this section is often referred to as a CBB's process for ensuring that all elements of collection, processing, and storage have been evaluated and determined to meet established safety, potency, and quality criteria, and is suitable for distribution.

**Evidence:**

The CBB should discuss with inspectors the laws and regulations applicable to its activities.

**Example(s):**

The evaluation includes determination of donor eligibility as defined by the FDA for non-U.S. CBBs exporting CB units to the U.S. Refer to FDA's Guidance for Industry, Eligibility

Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm>.

**STANDARD:**

*E4.3 When the maternal medical and/or genetic screening history indicates potentially transmissible disease or when there is a positive or indeterminate communicable disease test result:*

*E4.3.1 The CB unit shall not be released unless the CBB Director or Medical Director and a representative from the QM Program give specific authorization for release of the ineligible CB unit in compliance with Applicable Law and documents the rationale for such authorization.*

*E4.3.2 There shall be documentation of the consent to use the ineligible CB unit from the transplant physician.*

*E4.3.3 CB units deemed ineligible as a result of donor screening or testing for risk for transmission of communicable disease shall be labeled with the appropriate biohazard and warning labels detailed in the Modified Circular of Information Biohazard and Warning Labeling table in Appendix II.*

**Explanation:**

This standard pertains to situations where use of an ineligible CB unit is permissible with urgent medical need based on the unavailability of another suitable donor.

**Example(s):**

There are a number of mechanisms that comply with the requirement to label products as biohazardous:

- When an infectious risk is determined by testing that was not completed at the time of cryopreservation, a CBB may choose to attach a Biohazard label to the CB unit and maintain it in quarantine storage. However, for CB units frozen with overwrap, attaching a tie tag can be impossible or at least problematic.
- When infectious disease testing is positive and the CB unit is retained, some CBBs may elect to place the Biohazard label in the accompanying records. One example would be the retention of hepatitis B core antibody reactive CB units with negative hepatitis B NAT testing.

**STANDARD:**

*E4.4 At the time of distribution to a Clinical Program, the CB unit bag shall be labeled as required in the Cord Blood Unit Labeling table in Appendix I.*

**Explanation:**

Information that is required to be attached to the CB unit must be attached securely with a tie tag. Accompanying information must be enclosed in a sealed package to accompany the CB unit.

Appendix I contains minimum guidelines; a CBB may choose to be more inclusive.

**STANDARD:**

*E4.5 A circular of information or package insert and instructions for handling, thawing, and using the CB unit, including short-term storage and preparation for administration, shall accompany the CB unit.*

**Explanation:**

The intent of this standard is to require that the CBB gives the Clinical Program information on how to handle and use the CB unit.

**Example(s):**

An example of handling is washing. A “Circular of Information for the Use of Cellular Therapy Products” document (prepared jointly by the AABB, American Association of Tissue Banks, American Red Cross, American Society for Blood and Marrow Transplantation, American Society for Apheresis, America’s Blood Centers, Foundation for the Accreditation of Cellular Therapy, ICCBBA, International Society for Cellular Therapy, and National Marrow Donor Program) contains information (including indications, contraindications, and cautions) that is suitable for this purpose. This document can be found on the FACT website at [www.factwebsite.org](http://www.factwebsite.org).

For U.S. CBBs that wish to submit a BLA, the FDA guidance, “*Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications*,” suggests validating a thawing process that results in the recovery of at least 70 percent of the viable nucleated cells present before cryopreservation. Instructions for this process should be provided to the Clinical Program if the thawing will take place at that facility.

Because there have been documented adverse events related to the administration of CB units containing red blood cells, the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration* require dilution and/or washing of cellular therapy products that have not been red cell reduced, and this practice is also recommended for products that have been red cell reduced. In the case of double CB transplants, the Clinical Program must wait to administer the second unit until it is determined that the first unit was administered safely with no adverse events. It is recommended that CBBs include these same instructions to Clinical Programs when distributing a CB unit for administration.

**STANDARD:**

*E4.6 If the Clinical Program lacks experience in handling CB units, a practice CB unit should be offered.*

*E4.6.1 The practice CB unit shall be clearly labeled as a CB unit not intended for administration.*

**Explanation:**

A CBB may offer CB units otherwise unsuitable for transplant to Clinical Programs not familiar with a thawing method or a particular CBB's CB unit for practice thaws. Requests for these CB units may also be submitted for training, competency, or validation purposes. The CB unit offered for these purposes must be clearly labeled that it is not intended for administration.

**STANDARD:**

*E4.7 The CB unit should be received by the Clinical Program prior to initiation of the recipient's preparative regimen unless approved by the transplant physician.*

**Explanation:**

Since there is minimal risk to the infant donor and CB shipment is elective, with CB administration it is possible to have the CB unit at the receiving facility prior to start of the transplant regimen. This allows the receiving center to evaluate the quality of the CB unit prior to starting the preparative regimen. It is appreciated that the CBB can only recommend this practice to the Clinical Program.

**STANDARD:**

**E5 TRANSPORTATION AND SHIPPING OF CRYOPRESERVED CORD BLOOD UNITS**

*E5.1 Procedures for transportation and shipping of cryopreserved CB units shall be designed and validated to protect the integrity of the CB unit and the health and safety of personnel.*

*E5.2 The transit time between the CBB and other facilities shall be minimized.*

*E5.2.1 There shall be written plans for alternative transportation or shipping in an emergency.*

**Explanation:**

Same day transport and shipping arrangements are encouraged. Accidental tipping or conditions adversely affecting a CB unit must be averted with prompt attention. CBBs should educate their couriers on how to handle the CB unit and the importance of preventing tipping.

Registries may perform distribution for CBBs and they are required to comply with this requirement.

**Example(s):**

An example of a plan for alternative transportation or shipping in an emergency is utilizing a different courier or flight.

**STANDARD:**

- E5.3 Cryopreserved CB units shall be transported or shipped in a liquid nitrogen-cooled dry shipper that contains adequate absorbed liquid nitrogen and has been validated to maintain a temperature of -150°C or colder for at least 48 hours beyond the expected time of arrival at the receiving facility.*
- E5.3.1 The dry shipper shall contain an electronic data logger that continuously monitors temperature throughout the transportation or shipping period.*
- E5.3.2 The transport or shipping methods shall conform to Applicable Law regarding the mode of transportation or shipping of such devices.*
- E5.3.3 The dry shipper shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transportation or shipping of biologic materials.*
- E5.3.4 The lid of the dry shipper and the lid of the outer container shall be secured.*
- E5.3.5 The outer container shall be labeled with the information required in the Cord Blood Unit Labeling table in Appendix I.*
- E5.4 The CBB shall have written policies and procedures to obtain the following data from the receiving facility about the CB unit upon receipt:*
- E5.4.1 Date and time of receipt.*
- E5.4.2 Integrity of the dry shipper.*
- E5.4.3 Verification of appropriate temperature range.*
- E5.4.4 Integrity of the CB unit.*
- E5.5 Once an unrelated CB unit has left the CBB premises, it shall not be returned to the general CBB inventory.*

**Explanation:**

Return of unrelated CB units is not permitted by these Standards in part as a protection for the CBB. Clinical Programs needs to be certain that they are prepared to accept responsibility for the package prior to its release from the CBB.

Receiving the data about the CB unit upon receipt from registries and/or the Clinical Program is acceptable. The CBB must have a process in place to at a minimum attempt to obtain the information from the program.

**Example(s):**

In the event that a patient dies or is considered no longer eligible for transplant, it is the Clinical Program's responsibility to have a plan on how to handle the CB unit.

**STANDARD:****E6 TRANSPORTATION AND SHIPPING RECORDS REQUIREMENTS**

- E6.1 Transportation and shipping records shall permit the tracking and tracing of the CB unit from the CBB to its final destination.*
- E6.2 A list identifying the CB unit, intended recipient, intended destination, transportation and shipping records, and any warnings and other associated documents enclosed in a package shall be included.*
- E6.3 Transportation and shipping records shall document:*
  - E6.3.1 The CBB responsible for transporting or shipping the CB unit.*
  - E6.3.2 The date and time of packaging of the CB unit at the CBB.*
  - E6.3.3 The date and time the package left the CBB.*
  - E6.3.4 The identity of the courier and tracking information.*
  - E6.3.5 The date and time of receipt of the package.*
  - E6.3.6 Maintenance of the temperature within the specified range throughout the period of transportation or shipment.*

**Example(s):**

Tracking information can be in multiple forms, including online or in paper format.

**STANDARD:****E7 CLINICAL OUTCOME DATA**

- E7.1 For every CB unit released for administration, the CBB shall maintain details of clinical outcomes as necessary to confirm that the procedures in use in the CBB provide a safe and effective product.*
  - E7.1.1 The CBB shall obtain this information directly from the Clinical Program or, if utilized, through a registry or outcomes database.*

**Explanation:**

It is understood that a CBB is not in control of the compliance of the Clinical Program in providing information such as outcome data. However, the CBB should make it clear in an agreement with the Clinical Program or outcomes registry that they are required to obtain this information for analysis of quality, safety, and efficacy and demonstrate diligence in obtaining a high percentage of at least Day 100 and one year outcome data.

If the CBB relies on a third party to collect this data, there must be a system for timely sharing of data (especially with critical CB unit problems at time of receipt at the Clinical Program or at time of administration) in order for the CBB to meet quality control requirements.



**STANDARD:**

*E7.2 The CBB shall have a policy or procedure to obtain the following information within the recommended time period for every CB unit released for administration:*

**Explanation:**

Agreements with Clinical Programs should require the Clinical Program to furnish outcome data in so far as they concern the safety, purity, and potency of the CB unit involved. Standards E7.2.1 through E7.2.7 are written with “should” because it is understood that obtaining the data depends on the Clinical Program; however, E7.2 is written with “shall” because the CBB is expected to make reasonable attempts to obtain the data.

**STANDARD:**

- E7.2.1 Cell yield results on the thawed CB unit should be reported to the CBB.*
- E7.2.2 Adverse events associated with administration of the CB unit should be reported to the CBB promptly in accordance with Applicable Law.*
- E7.2.3 Serious adverse events related to the CB unit should be reported to the CBB in accordance with Applicable Law.*
- E7.2.4 Time to neutrophil and platelet engraftment should be reported to the CBB.*
- E7.2.5 Survival rates should be reported to the CBB annually at a minimum.*
- E7.2.6 For allogeneic CB units only, data should include engraftment and chimerism.*
- E7.2.7 GVHD results should be reported to the CBB annually at a minimum.*

**Example(s):**

There are a variety of ways that chimerism and GVHD are reported by Clinical Programs. CBBs should keep track of as much information as they can regarding how the results were found. For example, if the Clinical Program provides the CBB with information on how it scored GVHD, the CBB should maintain that information.

**STANDARD:**

- E7.2.8 In the case of more than one graft product used for administration, the CBB should collect and document that information and, if possible, which product engrafted.*

**Explanation:**

It is recognized that CBBs are challenged in receiving complete outcome data in dual CB administration settings, especially where the CBB provides only one of the CB units used in the transplant. Outcome data is difficult for the CBB to interpret, because results can be skewed by possible interactions of the recipient and dynamics of engraftment of either of the CB units. It is important to document that the CB unit provided was part of a dual CB transplant and analyzed accordingly.

DRAFT

Label Element	Partial label	At completion of collection	Outer container labeling at transport or shipping from collection	At completion of processing prior to cryopreservation	At distribution to Clinical Program	Outer container labeling at distribution to Clinical Program
Unique numeric or alphanumeric identifier	F	F		F	F	
Proper name <sup>2</sup>	F	F	F	F	F	
Product modifiers and manipulations <sup>2</sup>				C	C	
Statement Related Donor <sup>1</sup>	T	T		F	F	
Statement "Autologous Use Only" <sup>1</sup>					T	
Statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use." <sup>5</sup>					T	
Statement "Rx Only" <sup>5</sup>					T	
Collection site identifier		F				
Date of collection		F		C	C	
Time of collection and time zone, if different from the CB Processing Facility		C				
Name and volume or concentration of additives				C	C	
Name and volume or concentration of anticoagulants		F		C	C	
Recommended storage temperature		T		F	F	
Donor name (Related CB units) <sup>1</sup>		F		F	F	
Recipient family or individual name and unique identifier, if known <sup>1</sup>		F		F	F	
Recipient's name and unique identifier (if unknown after processing prior to cryopreservation)					T	
Volume or weight of the CB unit at the end of collection				C	C	
Volume or weight of the CB unit at the end of processing				C	C	
Date of cryopreservation				C	C	
ABO group and Rh type				C	C	
HLA phenotype				C <sup>6</sup>	C	
Number of nucleated cells post processing				C	C	
Gender of CB unit infant donor				C	C	
Identity of the CBB <sup>3</sup>				F	F	
Statement "Properly Identify Intended Recipient and Product"					T	
Statement "For Use By Intended Recipient Only" (Allogeneic CB units) <sup>1</sup>					T	
A statement indicating that leukoreduction filters should not be used					T	
Statement "Do Not Irradiate"					T	
Statement "For Nonclinical Use Only" <sup>1</sup>					T	
Biohazard legend and/or warning labels (see Appendix II, Modified Circular of Information Biohazard and Warning Labeling Table) <sup>1</sup>		C		C	C	
Donor eligibility summary. See Appendix III.					C	
Date and time of distribution					C	F
Shipping facility name, address, phone number			F			F
Receiving facility name, address, phone number			F			F
Identity of person or position responsible for receipt of the shipment			F			F
Statement "Do Not X-Ray" <sup>4</sup>			F			F
Statements "Medical Specimen", "Handle With Care" <sup>4</sup>			F			F
Statement indicating Cord Blood for Transplantation						F
Shipper handling instructions <sup>4</sup>			F			F

<sup>1</sup>If applicable.

<sup>2</sup>Product proper names, modifiers, and manipulations are listed in Chapter Three of the *ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*. Available: <http://www.iccbba.org/standardterminology.pdf>

<sup>3</sup>If there are CBBs of the same name in multiple countries, the identifier must distinguish between the CBBs on the label.

<sup>4</sup>If CB unit is shipped.

<sup>5</sup>If required by Applicable Law.

<sup>6</sup>If known.

F=Affix, T=Attach or Affix, C=Accompany or Attach or Affix; minimum requirements only. A CBB may choose to be more inclusive.

Facilities who have fully implemented ISBT 128 labeling shall follow the ISBT 128 Standard for the location of information.

**Appendix II Modified Circular of Information Biohazard and Warning Labels**

		Status			Product Labels						
Title 21 CFR Citation <sup>F</sup>		All Donor Screening and Testing Completed	Abnormal Results of Donor Screening	Abnormal Results of Donor Testing	Donor is resident in country on USDA <sup>E</sup> BSE list OR Testing performed in non-CLIA-certified laboratory.	Urgent Medical Need	Biohazard Legend [per 21 CFR 1271.3(h)]	For Autologous Use Only	Not Evaluated for Infectious Substances	WARNING: Advise patient of communicable disease risks	WARNING: Reactive test results for (name of disease agent or disease)
<b>Donor Eligibility Determination Required [21 CFR 1271.45(b)]</b>											
1	Allogeneic donors with incomplete donor eligibility determination <sup>A,B</sup>	No	No	No	Yes	Yes		X			
2	Allogeneic donors found ineligible	Yes	No/Yes	Yes	NA	NA	X		X		X
	A first-degree or second-degree blood relative <sup>C</sup>	Yes	Yes	No	NA	NA	X		X		
	A first-degree or second-degree blood relative <sup>C</sup>	Yes	No/Yes	Yes	Yes	Yes	X		X		X
	Unrelated donor	Yes	Yes	No	Yes	Yes	X		X		X
	Unrelated donor (USA Regulation <sup>G</sup> )	Yes	No	No	Yes	Yes	X		X		
<b>Donor Eligibility Determination Not Required [21 CFR 1271.90(a)]</b>											
3	Autologous donors <sup>D</sup>	No	No	No				X			
	Autologous donor	Yes	No/Yes	Yes			X		X		X
	Autologous donor	Yes	Yes	No			X				

A. The donor eligibility must be finalized during or after the use of the cellular therapy product. The results must be communicated to the treating physician [21 CFR 1271.60(d)4].  
 B. Abnormal results of any screening or testing requires labeling as in item 2 in this table (21 CFR 1271.65 applies).  
 C. Notification of the recipient's and donor's physicians of abnormal screening and/or testing results is required.  
 D. Any abnormal donor screening or testing results (even though neither screening nor testing is mandated for this group of donors) require appropriate labeling [21 CFR 1271.90(b)].  
 E. USDA – United States Department of Agriculture.  
 F. USA Federal Register, Code of Federal Regulations, Part 1271, Human Cells, Tissues, and Cellular Based Products, Revised January 1, 2004.  
 G. Applies to any cord blood unit collected, processed, stored, transported or transplanted in the US.  
 Modified table from the *Circular of Information for the Use of Cellular Therapy Products*, AABB et al. 2009. This table was modified to account for issues unique to CB banking. For the current version, visit [www.factwebsite.org](http://www.factwebsite.org).

ACCOMPANYING DOCUMENTS AT DISTRIBUTION TO A CLINICAL PROGRAM

CB units shall be accompanied upon leaving the CBB with the elements detailed in the following table at a minimum as required by Applicable Law<sup>1</sup>:

Documentation	Allogeneic Donor-Eligible	Allogeneic Donor-Ineligible	Allogeneic Donor-Incomplete	Autologous Donor
Statement that the donor has been determined to be either eligible or ineligible, based upon results of donor screening and testing	X	X		
Summary of records used to make the donor-eligibility determination <sup>2</sup>	X	X		
Name and address of the establishment that made the donor-eligibility determination	X	X		
Listing and interpretation of the results of all communicable disease screening and testing performed	X	X	X	X
Identification of the laboratory performing communicable disease testing meeting regulatory requirements. <sup>3</sup>	X	If applicable	If applicable	If applicable
Documentation of notification of the physician using the product of the results of all testing and screening	X	X	X	X (testing only)
Statement that the donor-eligibility determination has not been completed			X	
Listing of any required screening or testing that has not yet been completed			X	
Documentation that donor eligibility was completed during or after use of the CB unit and that the physician using the CB unit was informed of the results of that determination.			X	
Instructions for use to prevent the introduction, transmission, or spread of communicable diseases	X	X	X	X

<sup>1</sup> All elements are required for CB units manufactured in or designated for use in the U.S.

<sup>2</sup> Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

<sup>3</sup> Includes laboratories certified under CLIA of 1988, as amended from time to time, or those that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services.

## TESTING REQUIREMENTS

Specifications and Tests	Sample to be Tested			
	Fresh sample of CB obtained and tested after processing prior to cryopreservation	Fresh or frozen sample of CB tested any time before listing <sup>2</sup>	Cryopreserved post-processing sample of CB tested before release to the Clinical Program	Maternal sample obtained within seven (7) days before or after CB collection
Cell Count				
Total nucleated cell count	X			
CBC with differential	X			
Nucleated red blood cell count	X			
Viability				
Total viability	X			
Viable CD34	X			
CFU or other validated potency assay	X		X <sup>1</sup>	
Microbial culture	X			
ABO/Rh		X		
HLA				
Low resolution: HLA-A, B, DRB1		X (unrelated)		
High resolution: HLA-A, B, C, DRB1			X (contiguous segment – related and unrelated)	
Hemoglobinopathy			X	
Infectious Disease				
HIV 1		X <sup>6</sup>		X
HIV 2		X <sup>6</sup>		X
Hepatitis B		X <sup>6</sup>		X
Hepatitis C		X <sup>6</sup>		X
HTLV I		X <sup>5,6</sup>		X <sup>4,5</sup>
HTLV II		X <sup>5,6</sup>		X <sup>4,5</sup>
Syphilis		X <sup>6</sup>		X
Chagas		X <sup>6</sup>		X <sup>4</sup>
West Nile Virus		X <sup>6</sup>		X <sup>4</sup>
CMV		X <sup>6</sup>		X
Additional tests <sup>4</sup>		X <sup>6</sup>		X

<sup>1</sup>Recommended. For potency testing, testing is recommended prior to release; however, if post-processing testing was not performed historically, a potency assay must be performed prior to release for administration by the CBB or Clinical Program.

<sup>2</sup>In the U.S., the CBB may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease. Refer to the CBER website ([fda.gov/BiologicsBloodVaccines](http://fda.gov/BiologicsBloodVaccines)) for a list of approved tests. Testing is performed following manufacturer's instructions using FDA-licensed, approved, or cleared donor screening tests for relevant communicable disease agents and diseases (RCDADs) as defined by U.S. FDA. FDA-licensed, approved, or cleared donor screening tests are available for WNV and HBV NAT and T. Cruzi testing may be implemented per facility-specific guidance prior to an FDA testing requirement.

<sup>3</sup>In Europe, member countries of the European Union may amend and/or introduce additional requirements. In some settings, testing by more than one method may be required for some infectious agents. This table is not intended to reflect all national variations but rather present general requirements within the EU. The tests must be carried out by a qualified laboratory, authorized as a testing center by the competent authority in the Member State, using CE-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge.

<sup>4</sup>Additional tests for infectious transmissible agents may be required in accordance with Applicable Law or institutional policy. In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g., toxoplasma, CMV, EBV, *Trypanosoma cruzi*, etc.) and may include emergent disease testing.

<sup>5</sup>In Europe, HTLV I is performed only on a selected donor population with increased risk of infection and HTLV II is not required per EU Directive.

<sup>6</sup>Each CB unit should be tested for evidence of infection for communicable disease agents using licensed donor screening tests when available according to Applicable Law. Per the EU Directive, required maternal testing is repeated on the CB unit if stored for a long period of time, or alternatively NAT technology is used. This testing must be performed prior to release for administration when testing is required by Applicable Law or institutional policy.

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